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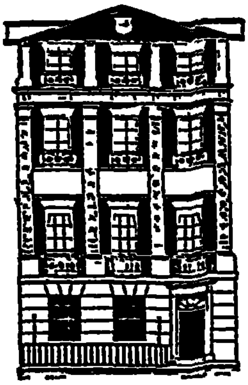

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LATION OF BODY TEMPERATURE IN HEALTH AND DISEASE*

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perhaps appropriate that, on the second day that y to preparing this lecture, I was decanted from lane at 8 A M in Labrador at a temperature of at 9 P M in Trinidad at a temperature of 90°F personal experience I was forcibly reminded of remarkable of scientific prophecies "La fixite du térieur est la condition de la vie libre"

entific generalisations can have proved so ng It occurs in *Leçons sur les phenomenes de la* ues given by Claude Bernard at the College of vo years before he died and published post- in 1878 Bernard had come gradually to his the constancy of the internal environment and tance to the organism In his well-known work mental medicine published in 1865,[1] he discussed ancy of the *milieu intérieur* and listed these emical components water content, temperature, gen, nitrogen, and CO_2), pressure, and chemical ion

ntext of the quotation from the 1878 work is as Bernard divided all life into three forms (1) "la manifestee", (2) "la vie oscillante, vie a manivariables et dependantes du milieu exterieur", "la vie constante, vie à manifestations libres et antes du milieu exterieur" Latent life is ed by seeds which lie dormant for long periods nder suitable conditions of temperature and they germinate, and in the animal world by nd eels, which may also remain dormant for long n ice, becoming active again when the ice thaws g life is exemplified by nearly all plants (partion-tropical plants), whose activity is dependent n, and by all cold-blooded animals Only those which are warm-blooded are independent of their urroundings They exemplify the third and orm of life The perpetual changes of cosmic ent do not penetrate into the animal, it is free pendent. Then Bernard goes on "La fixite du nterieur est la condition de la vie libre, ante"

is leaves us in no doubt as to the biological ce of the regulation of body temperature In this propose to discuss how this is achieved in a nan, and in the next how the mechanism is rough, or disturbed, in disease I shall concene on the nature of the regulating mechanism and e balance-sheet of heat production and heat loss, is adequately covered in contemporary and recent Finally in this lecture, to get perspective, I shall briefly the main features of the mechanisms another physical quantity, arterial pressure, mical quantity, blood-glucose

What are the Parts of the Body whose Temperature is Regulated?

It is an old observation, antedating accurate measurement, that the temperature of the extremities varies much with that of the environment The idea of constancy of internal temperature arose from measurements of temperature in the mouth, the axilla, the groin, the vagina, and the rectum More detailed exploration was undertaken by (among others) Claude Bernard, who confirmed that the venous blood leaving the limbs was cooler than the arterial, and that this difference was greater the lower the environmental temperature He also showed that blood in the inferior vena cava above the hepatic veins was warmer than that in the arteries, and that blood in the right heart was about 0 2°C higher than in the left, and thus in the aorta Thus the liver contributes materially to heat production and the skin and limbs to heat loss More recently Eichna et al (1951) have repeated these measurements in man and found the following deviations from rectal temperature

Pulmonary artery	−0 26°C
Right ventricle	−0 23°C
Inferior vena cava	−0 26°C
Hepatic veins deep in the liver	−0 03°C

In man, temperatures taken simultaneously from mouth, axilla, and rectum seldom differ from one another by more than 1°C, usually by less Of these the rectal temperature tends systematically to be the highest, and, because of the greater possibilities for heat loss from the other sites, it has in the past been regarded as the best index to arterial blood temperature Recent observations show, however, that its behaviour may be misleading in three ways

1 When the blood is quickly heated or cooled, mouth temperature reflects these changes quickly and in some circumstances nearly quantitatively, while rectal temperature may remain unchanged (Gerbrandy et al 1954) It follows that, if one is interested in rapid change in arterial blood temperature, the rectum is a bad place from which to estimate it As we shall see, ignorance of this fact led me astray many years ago

2 Comparison of aortic and rectal temperatures in people who have had grafting operations on the aorta shows that under ordinary environmental conditions rectal temperature tends to be about 0 3°C higher than aortic temperature (Cooper and Kenyon 1957)

3 The relatively high temperature of the rectum suggests that it may be a source of heat production The most likely cause is bacterial metabolism in fæces, but oddly enough this has never been investigated

So far as our present purpose is concerned, the conclusion of this section seems to be that the temperature whose constancy is being maintained is that of the deeper regions of the trunk and head I shall refer to this as the central body temperature This conclusion is of considerable relevance to the nature of the thermotaxic mechanism, as I hope later to show

How Accurate is Temperature Control?

Fig 1 is taken from the late Sir Charles Martin's Croonian lectures delivered twenty-seven years ago (Martin 1930) It shows the body temperatures of five species of animal after they had been exposed for two hours to temperatures from 5°C to 35°C At one extreme is the lizard, a cold-blooded animal whose temperature closely reflects that of its surroundings At the other is the cat, whose temperature is nearly independent of its

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oonian lectures for 1957, delivered on May 14 and 16 the Royal College of Physicians of London

y in the Royal Society of Medicine library is inscribed ghtingale", and the notes in the same hand at the end that she had read it

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environment The primitive mammals—the egg-laying echidna and ornithorhynchus, and the pouched opossum—occupy intermediate positions In man the mean rectal temperature has been stated to be 98 2°F (36 8° C) with a variation over the course of a day from a minimum of 97°F (36 1°C) at about 3 A M to a maximum of 99 3°F (37 4°C) at about 5 P M, giving a daily variation of 2 3°F (1 3°C) (Pembrey 1905)

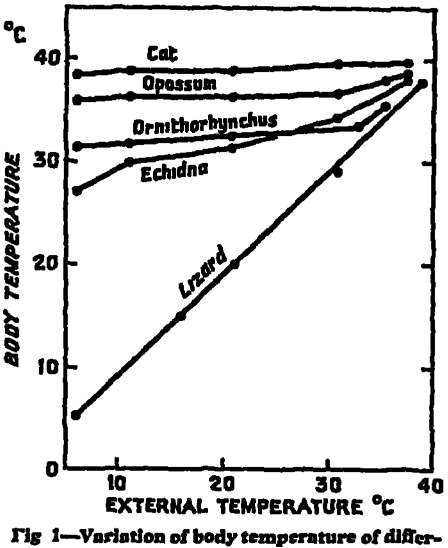

Fig 1—Variation of body temperature of different species of animals after two hours in environmental temperatures of from 5°C to 35 C (Martin 1930)

Ivy (1944) measured the mouth temperatures of 276 medical students seated in class in Chicago between 8 and 9 A M The mean was 98 1°F 68% were between 97 7° and 98 5°F, 95% between 97 3° and 98 9°F In statistical terms the mean is thus 98 1±0 4°F

These limits of variation are relatively narrow, whether we look at the variations in an individual or between individuals Indeed, Pearl (1940) concluded that the coefficient of variation of body temperature is one of the smallest for which quantitative human data are available Evidently the homœostatic mechanism concerned with temperature regulation is notable for its efficiency)

What is the Function of Temperature Control?

This was, as we have seen, discussed by Bernard Temperature control made the organism independent of its external environment Without it, the animal would be relatively, or nearly completely, inactive at low temperatures The rate of a chemical reaction is in general proportional to the absolute temperature As Sir Joseph Barcroft (1934) showed, certain reactions in the body—for example, the union of oxygen and hæmoglobin—obey Arrhenius' law, but several enzyme systems, and such functions as heart-rate and cilia-rate in cold-blooded animals, depart materially from it, the rate of increase being less than would be expected from Arrhenius' law at temperatures approaching 37–40°C

Not all warm-blooded animals are adjusted to the same temperature as man Most birds are higher, having normally a rectal temperature of about 42°C (Lefevre 1911) Among mammals the dog and rabbit normally have a temperature of 39–40°C

I am not familiar with any naturally occurring circumstances in which a temperature lower than 37°C confers an advantage on man, though modern surgery may profit Higher temperatures occur in fever, where their usefulness still remains to be demonstrated Athletes commonly warm up before a race Whether their accession of speed is due to rise of central temperature or to the effect of raised muscle temperature on its properties and performance I do not know, but the latter seems the probable

As Barcroft pointed out, one of the chief ills of high or low body temperature is *manifested by the* for consciousness tends to become clouded and later

Balance of Heat Production and Heat Loss

The temperature of the body, taken as a whole, determined by the balance between heat production heat loss Heat production consists of what one regard as obligatory and adjustable components obligatory component comprises the heat production muscle, liver, heart, and other organs carrying out th ordinary functions, whether the organism be at rest or full activity This part of heat production is not a of the device that regulates body temperature, in f it is the function of the device so to *adjust the oth* mechanisms that this component of heat production allowed for The adjustable component of heat produc tion, that which is a part of the mechanism regulating b temperature, is represented by shivering—i e, involunta contractions of voluntary muscle mediated through t motor nerves, and brought into play as a reser mechanism to maintain or raise body temperature

Heat loss is of course intimately dependent on enviro mental conditions, and, since in this age of technolog warfare the range of conditions to which man is expo *has been greatly widened, much research is being dev* to it If we ignore the changes due to intake of food drink, which are ordinarily small, the chief modes of he loss are (1) from the respiratory tract, by warming inspire air and by evaporation, and (2) from the skin, by radiatio conduction, and convection, by insensible water loss, a by sweating The dependence of all of these on th environment has been mentioned Man himself ca control the blood-flow through the skin and thus heat lo from it by radiation, conduction, and convection, and h can control sweating These are the essential com ponents, so far as heat loss is concerned, of the heat regulating mechanism

Birds and furred animals also use their coats to regula heat loss, some having different fur and feathers in winte and summer, and all being able to vary the thickness o the layer of air trapped by the coat to suit environmenta circumstances Dogs and certain other animals increas their heat loss largely by panting, the tongue and th respiratory tract being the surface Finally, man ha adopted clothing However, not all of us have been s enterprising Here is an extract from the diary of Charle Darwin for Feb 25, 1834, when H M S *Beagle* wa visiting Tierra del Fuego

> "Whilst going on shore, we pulled *alongside a canoe* w 6 Fuegians I never saw more miserable creatures, stunted i their growth, their hideous faces bedaubed with *white* pa & quite naked One full aged woman absolutely so, the rain spray were dripping from her body *Their red skins* filth greasy, their hair entangled, their voices discordant, the gesticulation violent & without any dignity Viewing such men, one can hardly make oneself believe that they are fellow *creatures placed in the same world* "

Twentieth-century civilisation has reached its fines flower in the American way of life Bertrand Russell ha pointed out that, whereas the older Western civilisation believe that man's function is to adapt himself to h environment, the modern American believes that it man's function to adapt his environment to suit himself Central heating, air-conditioning, and the automobile ıtrive to expose the heat-regulating mechanism of the ıdern American to less strain than perhaps mankind ; known through the ages To the "fixité du milieu ıerieur," modern man is adding the "fixité du milieu térieur"

To summarise, the effector part of the thermotaxic :chanism in man has two parts Heat production can increased by shivering Heat loss can be varied by rying the blood-flow through the skin, and increased by eating Variations in skin blood-flow provide the finer justments of temperature, shivering is called in by tremes of cold, and sweating by extremes of heat All ese effector mechanisms are under nervous control—ivering through the motor nerves, skin blood-flow and eating through sympathetic fibres In other warm-ooded animals panting is added as a defence against heat, ıd piloerection against cold These mechanisms are so under the control of the nervous system

Reflex and Central Control

Now we come to that aspect of the subject wherein has in my own chief interest How is the effector side tivated? Whence, in other words, comes the informa-on that leads to the opening and shutting of the arterio-nous anastomoses of the fingers, to the secretion of eat, to the erection of the hairs, and to shivering? In e past it has been usual to distinguish between reflex d central control Now, the concept of a reflex is quite ear I cannot do better than quote the master himself, r Charles Sherrington (1947)

> "The conception of a reflex therefore embraces that of at ast three separable structures—an *effector* organ—e g , gland lls or muscle cells, a conducting nervous path or *conductor* ading to that organ, and an initiating organ or *receptor* whence e reaction starts The conductor consists, in the reactions hich we have to study, of at least two nerve-cells—one con-cted with the receptor, the other with the effector For our rpose the receptor is best included as a part of the nervous stem, and so it is convenient to speak of the whole chain of ructures—receptor, conductor, and effector—as a *reflex-arc* '-A simple reflex is probably a purely abstract conception cause all parts of the nervous system are connected together d no part of it is probably ever capable of reaction without fecting and being affected by various other parts, and it is a stem certainly never absolutely at rest"

To most people central control implies the activity of a entre The idea of a centre is, compared with the idea f a reflex, much less precise It developed, I suppose, rgely to explain respiration Here was a rhythmic scharge of the central nervous system which ceased hen the brain stem was severed in the region of the ourth ventricle This was most easily explained by the resence in that region of a "centre"—i e , a group of erve-cells endowed with autonomous rhythm which ould, however, be modified by sensory reflexes and by hanging the content of carbon dioxide and oxygen in the spired air and thus in the arterial blood It proved onvenient to invent other centres—the vasomotor centre, he cardioaccelerator centre, the cardioinhibitory centre, nd the temperature centre—according to whether func-ion was lost abruptly by ablation of a specific part of the ervous system, or the appropriate activity evoked by imulating it Perhaps this was a feature of the anthropomorphic age of biological science At any rate it always eemed to me that what were called the lower centres of the brain were occupied by a lot of little men each with a quite specific job to do Many of these centres have now passed into the limbo of discarded ideas—e g , the diabetic centre of Claude Bernard, the vomiting centre, and the cardioaccelerator and cardioinhibitory centres The phenomena to which their conception was due can be explained either because the mechanisms concerned involve tracts with a finite and specific cephalad extension or else because of the location of a specific motor nucleus Nevertheless the respiratory centre remains, though somewhat shorn of its former powers It was believed to be autonomous, now it is believed that it is actuated by the hydrogen-ion concentration of certain cells of the medulla It was believed to be sensitive to arterial oxygen tension, now sensitivity to oxygen is known to be largely localised in the carotid and aortic bodies, whose receptors influence the respiration reflexly

Those who use the term " temperature centre " usually imply that it is sensitive to changes in temperature, and that in this quality, and the homœostatic effects so evoked, lies its peculiarity Functionally it is therefore rather a receptor than a centre, and because I have long thought that the concept of centres was not only imprecise but misleading I intend to use the term " central receptor " and not the term " centre " to describe that central structure or structures that respond to temperature with the appropriate homœostatic effects

Control of Vasomotor Tone in the Skin

Such, though some of the detail is new, was the background against which I saw the problem when I was first introduced to it It was my second year working with Sir Thomas Lewis Lewis had the idea that heating the body might produce a vasodilatation in the limbs, accessible to measurement by skin temperature, which might demonstrate the presence and extent of organic vascular disease We built a chamber that would enclose the trunk and in which the air could be heated by electric-light bulbs We showed that heating the trunk did in fact produce vasodilatation in the limbs , that this vasodilatation began first, and was most intense, in those parts of the hand that contained arteriovenous anastomoses , and that this vasodilatation was effected through the sympathetic nerves We found that the rate of rise and the final temperatures reached were less in patients with organic vascular disease We also obtained evidence that suggested to us the presence of vasodilator nerves, using an extremely sensitive preparation—namely, the patient with Raynaud's disease Subsequently I myself (Pickering 1936), Arnott and MacFie (1948), and Gaskell (1956) have observed that blood-flows through the hand and fingers are not significantly different in normal subjects when the body is heated, with or without previous anæsthetisation of nerves This has been interpreted to mean that the conclusions Lewis and I drew were wrong I prefer to think that it is a quantitative question, and that vasomotor nerves to the hand are quantitatively of little significance As Grant and Holling (1938) showed conclusively, they are much more important in the skin of the forearm

In view of the long controversy concerning vasodilator nerves to the hand, I think I should make my position quite clear It seems unlikely that the patient with Raynaud's disease is peculiar in her quota of vasodilator and vasoconstrictor fibres Rather is it likely that the obliterative lesions of the palmar arch and digital arteries —the basis of severe Raynaud's disease—make vasodilatation difficult in the cold hand and thus reveal that additional vascular dilatation that can be provided by stimulation of vasodilator nerves In the normal hand, where the digital arteries are patent, the vasodilatation produced by release of vasoconstrictor tone is so nearly maximal that any extra provided by vasodilator nerves cannot be detected Hess and I (1933) showed that, as measured by skin temperature, vasodilatation begins later in the foot than in the hand, and we provided evidence that this is due to incomplete release of vasoconstrictor tone in the foot, an explanation that harmonises well with the greater therapeutic effect of sympathectomy in the lower than the upper extremity

Interesting though this all was, I must confess that I was much more interested in how heating the trunk produced vasodilatation There were clearly two possibilities—namely, a reflex from the heated skin, or activation of some central structure by the hot blood returning from it Now, I had spent the year before working with Lewis on the effects of occluding the limb circulation on the pain of muscular exercise, and on nerve conduction I should have been an inept pupil if I had not realised that here lay a method that would answer the question Accordingly, when Lewis was on holiday, I set to work to see whether heating the arm whose circulation was arrested would or would not produce vasodilatation in the other

The difficulty was to get conditions right, for anyone who has worked with skin-temperature knows that conditions are broadly of three kinds (1) when environmental temperature is so high that the extremities are persistently vasodilated, (2) when the environmental temperature is so low that the extremities are persistently vasoconstricted, and (3) an intermediate zone in which finger temperature is extremely labile and the relationship between stimulus and response hard to establish

I used a cool room and subjects in whom the finger temperature had been raised to 34°C by heating in the hot box After the fingers had come out of the box, their temperature fell, and, when it was about 27°C, the other arm was immersed at 44°C with and without the circulation arrested With circulatory arrest, the skin temperature of the other hand continued to fall, until the circulation was released some minutes after release of the circulation a vasodilatation similar to that produced by the hot box ensued The method was, however, an unsatisfactory one,[2] since the time at which skin temperature rises when vasomotor tone is relaxed is greatly affected by local temperature, variations in skin temperature do not therefore accurately reflect the finer variations in vasomotor tone I therefore changed to Stewart's calorimeter, in which the heat eliminati from a hand or foot is measured, using water at 30°C—a te perature at which the hand vessels are neither unduly co stricted nor dilated This method is very robust and reliab but it is rather slow and does not detect rapid and transi effects

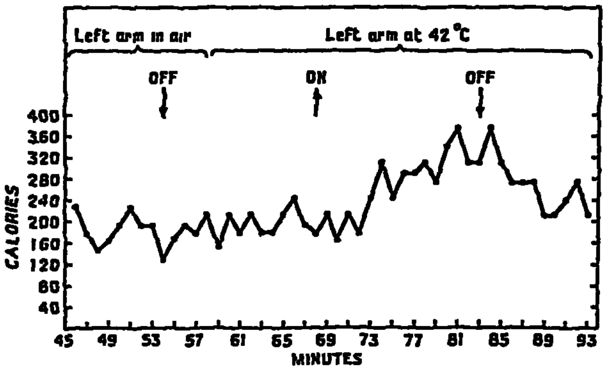

Fig 2—Elimination of heat from right hand Left arm was wrapped in cotton-wool till 59th min., when it was immersed in stirred water at 42 C. *Off* circulation to left arm arrested *On* circulation to left arm released Room temperature 21 5 C (Pickering *Heart*, 1932)

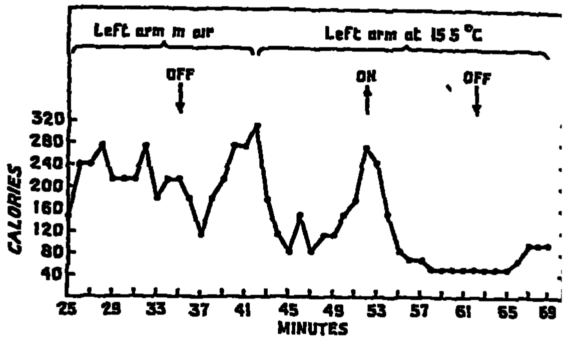

Fig 3—Elimination of heat from right hand Left arm was first air and its circulation arrested at 35th min (*Off*) It was immer in water at 15 5°C at 42nd min and its circulation released at 52 min. (*On*) (Pickering, *Heart*, 1932)

I found that, when one arm is immersed at 37°C, arresting t circulation to it induced no change in blood-flow in the oth hand, if the arm with arrested blood-flow was now immers in stirred water at 43°C, a transient vasoconstriction, but vasodilatation, occurred, when the circulation to the hot ar was released, nothing happened for a few minutes, and then vigorous dilatation began and persisted during the immersi (fig 2) Clearly the vasodilatation following the immersion an arm in hot water was not a reflex from thermal receptors the skin It arose in some way from the effect of h blood returning from the limb and acting on a more cent receptor

Cold provided a conspicuous contrast (fig 3) When t occluded limb was immersed in cold water, a vigorous vas constriction began in the opposite hand, but, as the lim remained immersed, the sensation of cold diminished, presum ably as the thermal receptors became adapted to the stimuli and coincidentally the vasoconstriction diminished If now th circulation was released, after a minute or two the vas constriction began again and this time persisted Cold clear differs from heat in that it produces a powerful vasomoto response reflexly from the receptors of the skin, it resembl heat in that a further vasomotor response is produced by co blood leaving the limb and acting on a central structur Similar phenomena were observed when the leg was immers in hot or cold water, or when heat elimination was measur from the foot during immersion of the hand

The phenomena which I had observed were not unli those observed before, but the procedure of circulator arrest enabled analysis to be made of the nature and si of the receptors initiating the reflexes

Vasoconstriction in one hand in response to immersing th other was first observed by Edwards, wrongly suppo to be confined to the symmetrical limb by Tholozan and Brow Séquard (1858), and correctly demonstrated to be a reflex b François-Franck (1876), the latent period being three second François-Franck also found that the reflex exhibited fatigue o repetition Stewart (1912), using his calorimeter, showed tha immersion of one arm in cold or hot water produced in th other hand a fall or a rise respectively in heat elimination, th former quickly, the latter only after a delay Although wi Laffer (1913) he obtained responses from the insensitive limb a patient with peripheral neuritis, he never questioned the re nature of the response Nor did Winkler (1902), who fo that, in rabbits with the spinal-cord transected, immersion o the insensitive hindquarters in hot water produced flushing o the ears only after a long delay, which he attributed to h time taken to warm the skin of the thermosensitive forequarte n view of Winkler's arguments, and doubt as to what d of thermal gradient would stimulate the thermal eptors in skin, it seemed desirable to see whether ular responses were obtainable from parts of the body irely devoid of thermoreceptors Such, as Hertz (1911) owed, is the stomach Introducing into the stomach, ough a tube, 400 ml of water at 20°C or 800 ml at °C led to the gradual onset respectively of a vasocon- iction and a vasodilatation in the hand, each lasting -30 minutes Water so introduced at 37°C and the culation of either cold or hot water through a tube rled up in the œsophagus were without effect

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[2] And I never published these observations on skin temperature because I never regarded them as being so conclusive as those with Stewart's calorimeter

Although, at the time when these experiments were ne, the idea of a temperature centre sensitive to changes blood temperature was being entertained, no real idence had been adduced for it, and cutaneous vaso- otor tone was widely believed to be controlled by lexes from the skin The new points arising from r experiments were (1) direct evidence for control of taneous tone by a central structure responding to anges in, presumably, blood temperature , and (2) the ggestion that this structure might be extremely sensi- e To see how sensitive it was, I measured rectal mperature, and this is where I went astray, because I und that the greatest change induced during a 10-minute riod of arm immersion was 0 1°C, and that, though I as using apparatus capable of detecting 0 01°C change, change in rectal temperature had occurred when the scular effect began) To check this I also measured the at gained or lost by the body to the hot or cold water which a hand was immersed at the instant the vascular sponse began in the other arm , about 2 6 kg cal had en gained or 1 3 kg cal lost by the body If this heat in or loss was distributed uniformly over the body, it emed that the sensitivity of the central structure would e of the order of 0 025–0 050°C

This estimate has subsequently been corrected by Snell d his colleagues, who found that, whereas similar nounts of heat had to be transferred in their experiments produce vasodilatation or vasoconstriction (Snell 1954), e change in mouth temperature was so large that it had be assumed that some structures in the body would ave their temperatures changed to the same extent as if he heat transfer were confined to the circulating blood- olume (Gerbrandy et al 1954) The sensitivity of the entral receptor is thus more probably about 0 2°C

I made one further set of experiments to test the idea hat a central receptor or receptors were concerned in ody-temperature control

It seemed to me that, if heat could be provided from within he body, no question of skin receptors would arise Accord- ngly I measured heat elimination from one hand while the ubject exercised on a stationary bicycle, rectal temperature eing measured thermoelectrically A typical result is illus- rated in fig 4, which shows the effects of three periods of xercise In each the onset of exercise is accompanied by vaso- onstriction in the hand In the first two periods, which are hort, vasoconstriction persists during exercise and is followed y vasodilatation In the third period, in which the work is ager and harder, vasodilatation begins during exercise and ersists after it

The vasoconstriction which marks the beginning of exercise 1 not been described in the hand but had been in the gut nd spleen by Sir Joseph Barcroft and his colleagues, and is in onformity with the other known phenomena occurring during is period The vasodilatation occurring either after exercise during its later stages is clearly compatible with the effects a rise of blood temperature Here I ran into difficulties

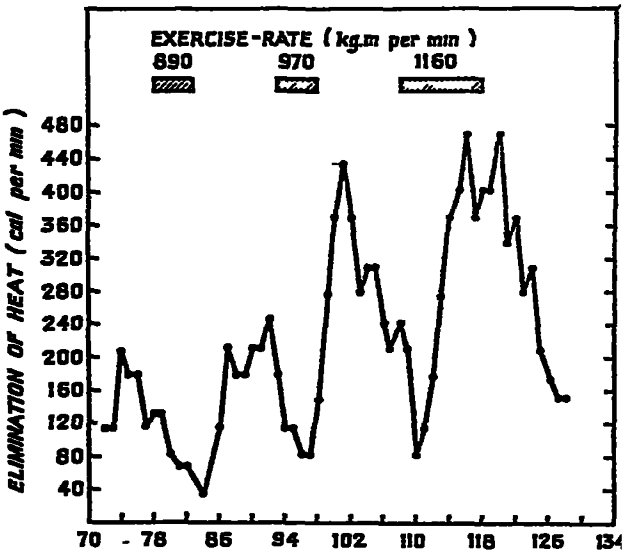

Fig 4—Elimination of heat from right hand during three periods of work on bicycle ergometer

I measured rectal temperature and got very unsatisfactory results, which I subsequently found were due to the body becoming electrically charged during exercise Before I could overcome this difficulty, my attention became diverted to the histamine headache and has since been fully occupied with other things

It is unfortunately impossible to calculate the heat gained or lost by the body during exercise of this kind, because the resting leg muscles are not at 37 C but at a lower temperature, and so an unknown fraction of heat production must go in internal redistribution of heat

Although these experiments did not enable a calculation to be made of the sensitivity of the central receptor, they were in conformity with its existence and behaviour suggested previously

I think I should apologise for having spent so long reliving an intellectual episode now more than a quarter of a century old Two reasons have impelled me to do so First, I am one of those who regard scientific research as an intellectual adventure that can provide the greatest excitement I know These were the first series of experiments in which the idea, the plan, and the execution were exclusively mine, and they have had that rather special place in my heart that a mother reserves for her firstborn Secondly these experiments and those subsequently made by Snell (1954) are the only ones which give any idea of the sensitivity of the central structure regulating vasomotor tone in man, and they indicate that it is very sensitive For this reason I have always wondered whether this structure may not be a specialised receptor[3] whence may pass impulses whose frequency determines the activity of the central nervous mechanisms governing heat production and heat loss In other words, there may be a central thermal receptor analogous to the baroreceptors of the carotid sinuses and aortic arch and to the osmoreceptors postulated by Verney

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[3] Most receptors are in fact nervous It may be that the temperature receptors are nerve-cells or nerve-endings located in the central nervous system Whether this be so or not if their activity is altered as a result of small changes in a specific environmental quantity (in this instance in the [illegible]) and if, as a result, complex motor effects are [illegible] through the central nervous system, then these structures are receptors in the ordinary sense

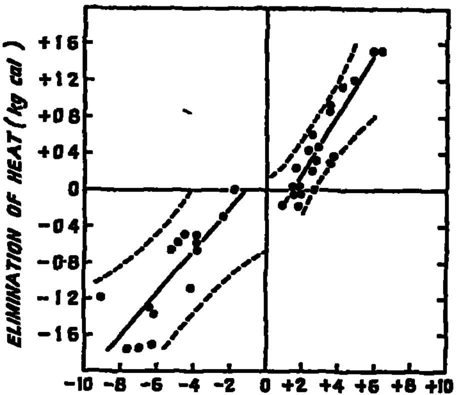

Fig 5—Relation between increase or decrease in elimination of heat from hand and amount of heat change producing it Stimulus was intravenous infusion of either hot or cold saline solution (Snell, *Journal of Physiology*, 1954)

The idea of a central structure responding to changes in blood temperature also occurred to Gibbon and Landis (1932), who shortly afterwards published experiments similar to mine and who also obtained vasodilatation in the hands by immersing in hot water the insensitive lower extremities of a patient with a transected spinal cord—the human counterpart of Winkler's experiments

Some of the most important evidence regarding the activity of the central receptor was provided by Snell (1954), who infused hot and cold saline solution intravenously in normal men and was thus able to measure accurately the heat transfer and the ensuing vascular response in the hand He found that the least heat transfers invariably causing vasoconstriction and vasodilatation were losses of 3 8 and gains of 2 4 kg calories respectively He further showed that there is a linear relationship between the sizes of heat transfer and vascular response of the hand, and that the slopes of the two regression lines for heat and cold do not differ significantly (fig 5) This would be consistent with the existence of a single set of receptors responding either to a rise or to a fall of blood temperature Furthermore Gerbrandy, Snell, and Cranston (1954) demonstrated a linear relationship between the size of the vascular response of the hand (in kg calories) and the area of the curve of mouth-temperature (in °C per minute), provoked by intravenous infusions of hot saline solution, though the rectal temperature is commonly uninfluenced This disposes of one of the main difficulties that other workers have found in recognising the activity of the central receptors, because they have usually measured, as I measured, the rectal temperature, and observed no clear relationship between changes in rectal temperature and changes in vasomotor tone

These experiments of mine were almost certainly misleading in the idea that they left about the importance of the temperature receptors in the skin Man is a terrestrial and not an aquatic animal, and the immersion of a part in very hot or very cold water, though a convenient laboratory device, is not a stimulus that we or our ancestors frequently encountered The vasoconstriction evoked is quite properly seen as merely an aspect of the vasoconstriction that follows any strong sensory stimulus (Hallion and Comte 1894)

Kerslake and Cooper (1950) found that exposing the trunk of a subject to radiant heat induced, after a latency of about 25 seconds, a rise in heart-rate and a vasodilatation in the hand They have shown that similar chang can be induced by so exposing the lower limbs, and th the responses persist when the circulation to the lowe limbs has been arrested The responses are unquestionably reflex Curiously they disappear when the lowe limbs are sympathectomised The receptors are thu probably not those that subserve the sensations of hea and cold

Now, there are two aspects of the behaviour of the receptors which require to be further explored becau they are so clearly important

The first, arising from Kerslake and Cooper's paper (195 is the suggestion that the reflex is not fatiguable, for irradiatin the trunk for 25 minutes gave vasodilatation persisting as long

The second, supported by the preliminary results of Coope Ferris, and Mottram (1956), is that there is a reflex vasoconstriction to exposure to a cold body, that the responses negative and positive radiation are quantitatively related to th radiant energy lost or gained, and that the lines relating the may be continuous

If these points are finally established, then it is clear tha we have to consider the activity of a set of receptors i the skin which are quite different from those ordinaril recognised and which may reasonably be supposed t have a profound effect on temperature regulation

To sum up, blood-flow through the skin and probabl of the mucous membranes of the mouth and nose (Mudd Goldman, and Grant 1921) is regulated partly by reflexe from receptors in the skin, probably different from thos serving sensation, and partly by the activation of a centra structure, perhaps a specialised receptor, that respon to changes in blood temperature of about 0 2°C

Control of Sweating

Leonard Hill (1921) first showed clearly that sweatin is under the control of a central temperature-sensiti mechanism He found that the sweating induced b sitting in a room at 38°C is stopped in a minute or tw by putting the hands under a cold tap If the circulatio to the arms was occluded, sweating did not stop unti after the pressure in the cuffs was released There wa no fall in rectal temperature, but calorimetric experimen showed that the rate of heat loss by the hands immerse in cold water was 0 6–1 2 kg cal per minute in t experiments

This, then, is a heat transfer of the same order as h been found to cause vasoconstriction A great deal o work has subsequently been done which shows a stro correlation between rate of sweating and deep sk temperature (Kerslake 1955) Since there is also a correl tion with rectal temperature, some have thought th sweating is controlled by receptors in the skin, and so by central receptors This is a very difficult problem skin blood-flow is in fact controlled by central temperatu receptors, and if sweating is similarly controlled, a corre tion between skin temperature and sweat-rate might b expected Hill's experiments still stand as the mo definitive

Control of Shivering

It is an old controversy whether the additional he production that can be evoked through the thermo regulating mechanism is or is not solely effected throu shivering Shivering is probably the main, if not the so mechanism Electromyographic records show that, first, the muscle units fire off at different frequencies out of phase with each other (Burton and Bronk 193 the discharges become phasic The former irregular raction has been called thermal muscular tone , the sic discharge constitutes shivering Cutting the terior roots abolishes shivering but not thermal tone nan shivering is mediated through the anterior roots, vated not by the pyramidal tracts but by the lateral ospinal or rubrospinal tracts (Uprus et al 1935)

ather less is known about the afferent side of control, it seems that the same two sets of receptors, peripheral central, are concerned It is a common experience t, if a subject is cold, either the sudden application of to the skin or a blast of cold air may induce shivering a few seconds—a time interval which is too short for er than a reflex from the skin On the other hand, if a ject is warm—e g , after exercise—the same stimuli y not produce shivering Experiments on dogs emingway 1939) on the whole support these impressions ned from man However, the strongest evidence for activity of a central thermosensitive mechanism was t provided by Sherrington (1924), who showed that mersion in cold water of the insentient hindquarters of log whose spinal cord was severed produced, after a ent period, shivering in the normally innervated fore-arters

Thermotaxic Centre

Evidence concerning the thermotaxic centre is of two ids—namely, loss of this function when parts of the ain are removed, and display of the relevant motor enomena when parts of the brain are stimulated, par-ularly by heat or cold

Isenschmid and Schnitzler (1914), by careful section of the ain stem in rabbits, showed that that part of the diencephalon uated in front of the posterior edge of the optic chiasma is necessary for heat regulation, and that the integrity of the ber cinereum is essential

Ranson and Ingram (1935) produced coagulation necrosis the brain stems of rhesus monkeys and allowed them to cover In seven monkeys the ability to protect against se of blood temperature was lost , in these the lesion was lateral in the rostral part of the anterior hypothalamus ne monkeys became cold when removed from the warm om , all three had bilateral lesions destroying the posterior rt of the lateral hypothalamus, in the region lateral to the amillary nuclei

Evidence for the spatial separation of centres protecting gainst overheating and overcooling was also obtained in the t by Clark, Magoun, and Ranson (1939) and in the dog by lair and Keller (1946)

A major difficulty in investigating the responsiveness of ie brain to changes in its temperature is the profound ffect of anæsthesia on the vascular system In man eneral anæsthesia is commonly associated with an icrease in skin blood-flow and a decrease in renal blood-ow (Lee et al 1953) In the dog Hemingway (1941) howed that pentobarbitone, amylobarbitone, and ether ll reduced the ability to protect against low temperatures

Kahn (1904) heated the carotid arteries of rabbits and its and observed flushing of the skin when the mouth-mperature had risen by 2°C Barbour (1912) circulated ater through a metal tube in the region of the corpus striatum ad found that 42 C was the lowest temperature that caused ushing, and 33 C the highest that caused paling, of the ears f rabbits These changes are clearly much too large to present the activities of the central receptors—at least as ey are known in man

Magoun et al (1938) introduced paired insulated 'Nichrom' ctrodes into the hypothalamus of cats under urethane esthesia with the Horsley-Clarke stereotaxic instrument and heated the region between them with a high-frequency diathermy current They found that heating an area of the hypothalamus dorsal and cephalad to the optic chiasma produced acceleration of respiration and sweating of the fore-pads Similar results were obtained in cats and dogs under nembutal, chloralose, and urethane anæsthesia by Folkow et al (1949) In cats the responsive region was 8 mm caudal to the anterior border of the optic chiasma In this region a temperature rise of not more than 0 5°C produced slight cutaneous vasodilatation after a latency of 15–20 seconds This is the strongest evidence concerning the location of a central temperature receptor

Hemingway et al (1940) had come to the same conclusion They placed gold electrodes on the ventral surface of the brain, anteriorly between the optic tracts and over the chiasma, and posteriorly between the pituitary stalk and mamillary bodies A month later shivering was induced by cold Heating the anterior electrode with a diathermy current stopped shivering , heating the posterior electrode did not

Ström (1950) systematically explored the hypothalamus of anæsthetised cats with one electrode cooled by water and failed to observe any alterations in cutaneous blood-flow or respiratory rate when the anterior or posterior hypothalamus was cooled to 31–36°C On the other hand, if the anterior hypothalamus was so cooled while heating by diathermy was in progress, the cutaneous heating produced by diathermy disappeared Cooling the carotid arteries was not effective in cooling the hypothalamus but produced vasoconstriction that was thought to be a reflex from cooling the facial skin

It has been very generally concluded from the destructive experiments that there are two thermotaxic centres one of which protects against cold while the other protects against heat In fact all the evidence displays is that the tracts subserving these two functions pass through different areas of the hypothalamus and can be separately interrupted The evidence that heating a quite local area of the hypothalamus produces changes that duplicate those elicited by exposing the body as a whole to heat is very strong evidence that this is the site of the central receptor responding to heat , as Folkow et al (1949) have shown, the rises of temperature are too small to represent a non-specific stimulus The evidence would be stronger if the same area had been shown to respond to cold, but this is much more difficult technically, and so far the sole evidence is Strom's (1950) observation that cold will inhibit the effects of heating

Thermotaxis as Example of Homœostasis

Having considered the parts, we may now try to view the whole, to see how the various mechanisms are integrated and coordinated to regulate body temperature As we have seen, there are three effector mechanisms in man—shivering, cutaneous vasoactivity, and sweating—which regulate heat production and heat loss All are effected through the nervous system, as are the other two devices of mammalia, polypnœa, and piloerection These effector mechanisms require the integrity of the central nervous system up to and including much of the hypothalamus We may assume that the nervous pathways extend cephalad to about this point in the central nervous system

So far the problem is non-controversial What is controversial is the way in which this mechanism is activated A commonly held view is that of Bazett (1949) supported by Burton and Edholm (1955) They consider that cutaneous reflexes play a dominant role and that the chief thermal receptors are those of the skin " There is no need to postulate a specialised ' thermal receptor ' in the brain, for which we have no histological evidence whatever '

They think that there is "definite evidence of the anatomical and physiological separation of the heat loss and heat conservation centres," and they think that the evidence that exists for some central control can be explained by the effect of temperature on the relaying and conducting functions of these centres

The evidence collected here leads me to think that this is not a correct assessment of the situation To my mind the evidence points strongly to the dominant role of the central receptor or receptors and the subsidiary role of the cutaneous receptors Whether the central receptors are situated in the hypothalamus or not is important but not essential to the concept These several receptors give rise to nervous impulses which are, no doubt, summated and integrated in the brain and excite the various efferent mechanisms

I think we can take it as established that the thermal receptors of the skin are concerned with temperature regulation By reason of their situation and of the reflex responses to which they give rise, they are most probably concerned in the immediate protection of the body against hot and cold environments For example, Sherrington (1924) noted that, when a normal dog was removed from its pen at 26 6°C to a cold room at 1°C, the vaginal temperature at the end of 40 minutes showed a slight rise Again, Kerslake and Cooper (1950) observed that, when the limbs or trunk are exposed to radiant heat, the reflex vasodilatation in the skin is regularly accompanied by a fall in mouth temperature In each of these two instances the actual change in central body temperature is the reverse of the environmental change; reflexes from the skin have overcompensated for the change in the *milieu extérieur* However, we still have a great deal to learn about the behaviour of these receptors I used to think that, as François-Franck (1876) first pointed out, they were easily fatigued It seems probable, however, that the receptors are not themselves responsible for sensation and their detailed behaviour, in so far as this is manifested by reflex changes, remains to be explored

I think we can take it as established that a central receptor or receptors are also concerned in temperature regulation; their activity has been demonstrated in the control of cutaneous vasomotor tone, of sweating, and of shivering

In considering the relative importance of these receptors one major fact stands out—namely, that the constancy achieved in the temperature of the central parts of the body is of a very high degree, whereas that of the skin is not This consideration alone makes it probable that the central receptors play a dominant, and the skin receptors a relatively subsidiary, role in the long-term regulation of temperature This case remains incomplete in the sense that the location of the central receptors is not yet proved, nor is it known by virtue of what physicochemical peculiarity they respond in the way that they seem to Thus, though there is suggestive evidence that areas in the hypothalamus close to the optic chiasma respond appropriately to a rise of temperature, there is virtually none that they respond to a fall Nor is there any evidence that these areas differ in their histological appearance from other cells of the hypothalamus (Eliasson and Strom 1950)

The concept of the mechanism regulating temperature in man developed here is thus as follows Small deviations in central body temperature are opposed by corresponding deviations in cutaneous vasomotor tone Larger deviations upward or downward are opposed respectively by sweating and by shivering The effector mechanisms are activated chiefly and persistently by central receptors, less importantly and intermittently by cutaneous receptors Coordination and integration take place within the central nervous system, probably in the hypothalamus or below The spinal tracts concerned in the control of shivering and vasomotor tone are probably different, and this may account for the way in which protection against heat and cold are differentially affected by localised hypothalamic lesions Except in this sense it is unlikely that there are different centres for the regulation against heat and cold

Comparison with Other Homœostatic Mechanisms

The concept here presented of the way in which the temperature of the *milieu intérieur* is regulated assigns a dominant role to receptors that appreciate changes in this milieu—receptors that may properly be called proprioceptors, as opposed to the exteroceptors of the skin To put this concept into perspective it may be compared with the mechanisms regulating blood-pressure and blood-sugar

Blood-pressure

The old concept of the regulation of blood-pressure was that both the peripheral resistance and the cardiac output were under the control of autonomous medullary centres—the vasomotor, cardioinhibitor, and cardio-accelerator centres (see Bayliss 1923) The activity of these centres was affected by impulses from the various sensory nerves and the higher centres, and by oxygen and carbon-dioxide content of the blood

It was always difficult on this concept to see how the blood-pressure was so nicely regulated However, the work of Hering and Heymans has shown how profoundly defective this concept was We now know that perhaps the most important regulators of blood-pressure are the baroreceptors of the carotid sinus and the aortic arch; alterations in pressure in these proprioceptors alter the number of impulses originating from them, and so lead to the reflex initiation of changes in heart-rate and vasomotor tone that tend to oppose the alteration The effector paths, including those to the adrenal medulla, are nervous, and the mechanism is thus almost a perfect analogue for that here presented as responsible for temperature control

In addition the renin-hypertensin system is probably concerned in the control of arterial pressure As to how that control is effected I have nothing material to add to what I presented fourteen years ago (Pickering 1943); it is, however, unlikely that a nervous mechanism is involved This mechanism, if it is indeed concerned in blood-pressure control, has no known analogue for temperature

Blood-sugar

The control of the blood-sugar level is quite different from either of the foregoing The first line of defence seems to be the taking up or discharge of glucose by the liver and muscles from or into the blood This control is effected largely through increase or decrease in the secretion of insulin by the pancreas, which is itself controlled by the sugar content of the blood perfusing it The second line of defence is the mobilisation of glucose from the liver due to the action of adrenaline, secreted in response to the effects of low blood-sugar level on the cells of the central nervous system

Here, then, we have a chemical quantity, regulated argely by chemical means—i e, by hormones, which are hemselves controlled by the blood-sugar

The principle in all these three examples is the same —i e, if a particular quantity in the *milieu interieur* is egulated within narrow limits, the regulating mechanism s chiefly activated by alterations in that quantity It eems to me not improbable that this principle is of quite eneral application

(*To be concluded*)

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"Few health workers have had a serious chronic illness and so the world of the patient is unfamiliar to them They may be familiar with his lungs, joints, blood pressure, or blood sugar concentration, but his outlook on life, likes and dislikes, private terrors, and feelings about his family can be as unfamiliar as the uncharted bottom of the sea The worker should remember that chronic illness *is* a way of life He must be careful and tender of feelings, but decisive and affirmative Patients are made more anxious by too passive an approach "—*Prevention of Chronic Illness* Commonwealth Fund Harvard University Press 1957

HYPERTENSION FOLLOWING X-IRRADIATION OF THE KIDNEYS

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FOR many years it has been known that X-irradiati may damage the kidneys, but the clinical importance this has been recognised only recently (Luxton 1953)

Schulz and Hoffmann (1905) were the first to study t histological changes in the kidney following experimen irradiation In rabbits they observed a great increase interstitial tissue, together with atrophy of the tubules a glomeruli which they attributed to compression by the n connective tissue The blood-pressure was not measured, b in one rabbit examined after 48 days (the longest period observation after irradiation) muscular hypertrophy of t renal vessels was noted

Hartman et al (1926) irradiated dogs' kidneys in si using high-voltage X-rays to avoid excessive damage to t abdominal wall They confirmed the earlier finding of a gre increase of connective tissue replacing the tubules t glomeruli were not decreased in number, but in dogs observ for more than 3 months after irradiation they exhibited vario degrees of hyaline atrophy Blood-vessels of all sizes in t kidney showed thickening of their walls and in many cas obliterating endarteritis Hypertension was noted in the long-standing cases, and death was usually due to renal failu Later the same workers (Hartman et al 1927) demonstrat hypertension, renal failure and histological lesions when o kidney of a dog was exteriorised and irradiated, the other bei removed and the rest of the body protected by lead O'Ha et al (1926) made similar observations in rabbits

Essentially the same findings were obtained in rats Bennett et al (1953), who used whole-body irradiation und anoxic conditions to lower the mortality-rate With a dosa of 600–1400r, nephrosclerosis and moderate hypertension we observed after 300 days

In man, evidence of renal damage was reported Warthin (1907) in patients irradiated for leukæmia Mu later

Dean and Abels (1944) described a most interesting ca of a woman, aged 20, with an abdominal mass who receiv 4600r to the left upper quadrant of her abdomen in 25 day 7 years later she was found to have hypertension with eviden of impaired function in the left kidney At operation th kidney was found to be shrunken and fibrotic, and after removal the blood-pressure returned to normal

Zuelzer et al (1950) reported a form of glomerulonephri in three children who had received therapeutic irradiati (5000–6850r in 4 months) to the renal area All of them di from renal failure and hypertension within 7 months of t first irradiation Renal changes included lesions of t glomerular capillaries and Bowman's capsule, tubular atrop and necrosis, and interstitial fibrosis, no blood-pressu measurements were recorded

The infrequency of such reports was no doubt due to t rarity of the conditions for which the upper abdomin areas were subjected to high-dosage irradiation

Luxton's series—the largest yet published—consist of patients who during treatment of testicular tumou received intensive irradiation (2300r in 5 weeks) over a wide field including both kidneys. Of those at risk, twenty-seven (about 20%) developed albuminuria, nearly all had hypertension, and in many there was renal impairment.

No serial studies of blood-pressure, urine, or renal function were made from the time of irradiation, because the renal complications were unexpected. Thus many of the cases could be reviewed only retrospectively. From the evidence available it appeared that the blood-pressure rose after an interval of at least 6–12 months after irradiation.

Luxton classified his series clinically into acute and chronic radiation nephritis and benign and malignant hypertension. In the two cases classified as malignant hypertension albuminuria was present when the urine was first examined, but one patient had normal renal function: both patients died within 7 weeks of the onset of symptoms.

Of the whole series seven patients died, and necropsy material from four was studied and reported fully by Russell (1953). In three necropsies on patients who presented with "acute radiation nephritis" the important histological lesions were thickening of the renal capsule, diffuse interstitial fibrosis, tubular degeneration, glomerular hyalinisation, arterial hypertrophy, and arteriolar hyaline necrosis. This picture is in nearly all respects similar to that described in laboratory animals. In one case presenting with malignant hypertension there was again widespread interstitial fibrosis, with a tendency to form dense wedges of sclerotic atrophy. Most of the glomeruli were abnormal and showed partial or complete hyalinisation and occasional hæmorrhagic infarction; the tubules were largely atrophic. Hyaline arteriosclerosis and endarteritis fibrosa of the interlobular arteries, and fibrinoid necrosis of arterioles, were present.

Luxton thought that fibrous thickening of the kidney capsule was a possible but unlikely cause of the hypertension, by analogy with the perinephritis observed when hypertension is produced in animals by enclosing the kidney in a 'Cellophane' capsule. However, in our studies of malignant hypertension at The London Hospital we have observed cases in which this syndrome followed irradiation of the kidneys, and in two instances there was an apparent dissociation between hypertension and irradiation sclerosis. In these, there was no evidence of diffuse interstitial fibrosis, glomerular hyalinisation, tubular atrophy, or severe thickening of the renal capsule. Indeed, the most significant histological changes in the kidneys were scattered arteriolar and glomerular necroses presenting a picture indistinguishable from that of early malignant essential hypertension.

These findings led us to the view that in certain circumstances irradiation of the kidneys might induce hypertension in the absence of irradiation sclerosis, and that in such cases renal structural changes might be predominantly secondary to the hypertension. In this paper we shall first describe two patients in whom hypertensive renal disease developed after irradiation, illustrating these two distinct patterns of renal structural damage. We shall then present a series of experimental studies in the rat, designed to clarify the relation between hypertension and structural changes in the kidney following irradiation.

Two Types of Hypertensive Renal Disease due to Irradiation of the Kidneys in Man

FIRST CASE

The first patient received deep X-ray therapy for an abdominal carcinoma and died 8 years later with hypertension and uræmia. The histological picture is the common type in which chronic irradiation sclerosis is associated with hypertensive renal lesions.

First Admission

A woman, aged 35, was admitted on March 31, 1946 (no. 40430). Swelling of her ankles had been noticed 6 weeks previously, followed by sudden pain in her right calf after 3 weeks and swelling of the whole limb.

Examination.—Signs of right femoral thrombosis; large firm upper abdominal mass, moderate ascites. Apex-beat not displaced. Blood-pressure 160/100 mm. Hg, falling to 120/80. Urine: sp. gr. 1·015, no albumin. Hb 88%, leucocytes 7300 (normal differential count). Wassermann reaction negative. Barium meal and chest radiograph normal. Intravenous pyelogram normal.

Laparotomy (April 3, 1946).—"Solid lobulated mass attached firmly to posterior abdominal wall, probably connected with pancreas." Microscopical report on biopsy specimen: "piece of pancreas, infiltrated by carcinoma composed of solid groups of small polygonal cells."

Deep X-ray therapy started on May 28, 1946. Upper abdominal baths, 3000r, 26 treatments in 35 days. During the next 12 months the ascites and abdominal mass gradually diminished. The patient ceased to attend hospital, and remained well for some years.

Second Admission (May 4, 1954)

Generalised aches and malaise for 2 weeks, and frequent vomiting for 3 days. Sallow complexion, pulse 110, neck veins distended, well-marked pulsation in suprasternal notch. Apex-beat in mid-axillary line. Heart sounds normal. *Blood-pressure* 190/115. Death occurred suddenly soon after admission.

Postmortem Findings

Kidneys contracted (left 3¼ oz., right 1½ oz.), granular subcapsular surface, cortex narrowed, arcuate arteries prominent. Great hypertrophy of left ventricle, considerable atheroma

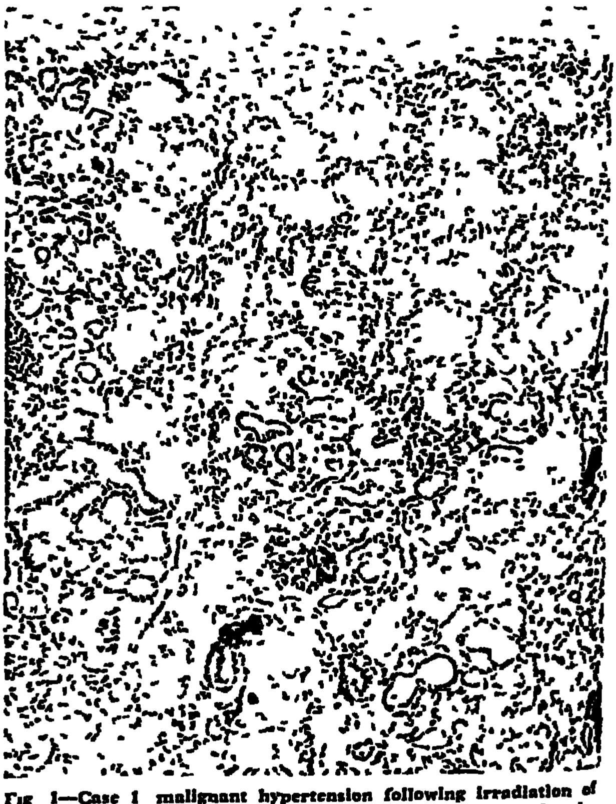

Fig. 1—Case 1: malignant hypertension following irradiation of kidneys: irradiation sclerosis of kidney. (Hæmatoxylin and eosin. × 57.)

Œdema of lungs Membrano-hæmorrhagic "uræmic" colitis No definite abnormality in or around pancreas

Histology of kidneys (fig 1)—Gross disorganisation of renal pattern, particularly in the smaller kidney, variable fibrous thickening of capsule

Glomeruli not significantly reduced in number, but more than half show hyaline degeneration of tuft and great collagenous thickening of Bowman's capsule Many hyaline glomeruli are aggregated in subcapsular areas of fibrosis (fig 1), but others are scattered throughout cortex Most other glomeruli appear normal, but a few show acute focal, sometimes hæmorrhagic, necrosis of tuft

Tubules very severe diffuse atrophy, with slight dilatation

Vessels frequent fibrinoid necrosis of afferent arterioles and interlobular arteries Endarteritis of some interlobular arteries, fibroelastic intimal thickening and medial hypertrophy of larger arteries

Interstitial tissue diffuse fibrosis, moderately cellular, with fairly uniform collagen deposition involving both cortex and medulla

This patient had a normal blood-pressure when, at the age of 35, she received irradiation to the upper abdomen over a wide field, including the kidneys When hypertension developed is unknown, because she was not observed until symptoms of uræmia appeared 8 years later The interstitial fibrosis, atrophy of the glomeruli with fibrosis of their capsules, and the changes in the larger arteries indicate a longstanding and slowly progressive nephrosclerosis Fibrinoid arterial and arteriolar necroses and glomerular necroses are evidence of terminal acute hypertensive renal damage In many ways these structural changes resemble malignant nephrosclerosis superimposed on benign nephrosclerosis, nevertheless in certain respects the picture differs from any other form of Bright's desease The features characteristic of irradiation nephrosclerosis are the diffuse interstitial fibrosis and the large numbers of fibrohyaline glomeruli, both aggregated in subcapsular fibrotic zones and diffusely scattered through the cortex

SECOND CASE

The second patient received deep X-ray therapy after orchidectomy for seminoma of testis and died 11 months later with hypertensive heart-failure and uræmia The histological picture is indistinguishable from that of early malignant essential hypertension

A man, aged 27, underwent right orchidectomy for seminoma of testis in October, 1947 Blood-pressure 140/90 mm Hg, urine normal From January to February, 1948, he was treated with deep X-ray therapy to para-aortic regions Upper abdominal baths, 3000r, 26 treatments in 36 days On Dec 18, 1948, he was admitted to The London Hospital (no 4285) complaining of severe breathlessness, weakness, and dimness of vision

Examination—Orthopnœic, Cheyne-Stokes respiration, blood-pressure 210/130, pulsus alternans Apex-beat 6th space in anterior axillary line, gallop rhythm, crepitations at left base, liver enlarged and tender, speen palpable Optic fundi bilateral papillœdema and exudates, distended veins, and narrowed arteries Urine albumin, trace to $^1/_4$ volume, sp gr 1 010, moderate number of granular casts and red blood-cells Blood-urea 150 rising to 270 mg per 100 ml Hb 34% X-ray of chest mottled shadows suggesting pulmonary œdema Condition deteriorated rapidly, death on Jan 4, 1949

Postmortem Findings

Kidneys not contracted (12 oz.), capsule adherent in parts, scattered petechiæ on subcapsular surface Great œdema of lungs, small pleural effusions Heart $17^1/_4$ oz, great hypertrophy and moderate dilatation of left ventricle, coronary arteries free from atheroma, moderate atheroma of aorta Œdema of liver and spleen No evidence of secondary growth

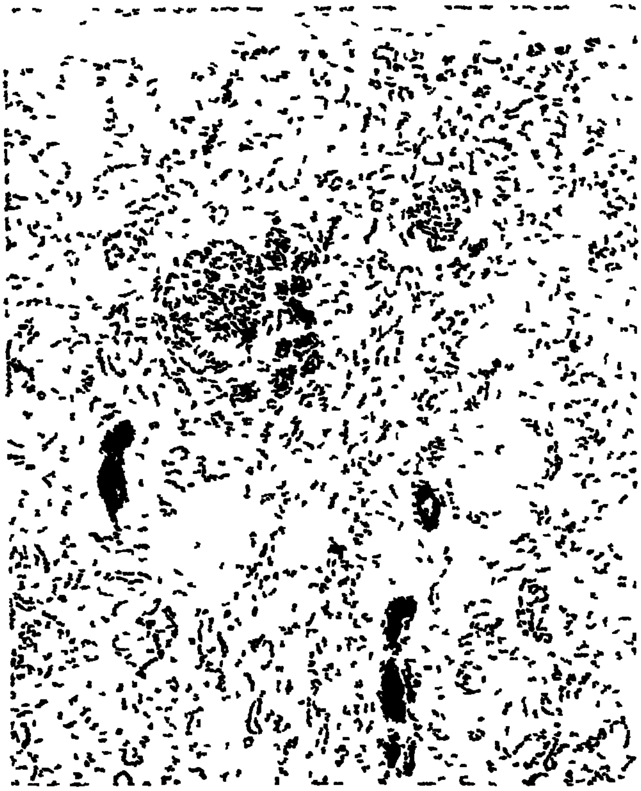

Fig 2—Case 2, malignant hypertension following irradiation of kidneys glomerular and arterial necrosis without irradiation sclerosis (Hæmatoxylin and eosin × 57)

Histology of kidneys (fig 2)—No distortion of renal pattern Focal subcapsular scarring with adhesion and thickening of renal capsule in these areas, but no general capsular fibrosis

Glomeruli not diminished in number, majority appear normal, but many show acute, often fibrinoid, sometimes hæmorrhagic necroses (fig 2) Capsular epithelial proliferation in a few glomeruli, early capsular fibrosis in others

Tubules not dilated, diffuse albuminous degeneration, severe in places, occasional hyaline droplet degeneration Some tubules contain red-cell aggregates, others altered blood

Vessels severe fibrinoid necrosis of scattered arterioles and interlobular arteries, no endarteritis Medial hypertrophy but only slight intimal elastic hyperplasia in larger arteries

Interstitial tissue diffusely increased in cortex and medulla owing largely to œdema, but with slight cellular proliferation, congestion of intertubular capillaries

This patient had a normal blood-pressure when, at the age of 28, he received irradiation to the renal areas He died of malignant hypertension less than a year later Histologically acute arterial and glomerular necroses are the most prominent lesions, a picture closely resembling malignant essential hypertension in its early stages The interstitial œdema could be explained by terminal heart-failure, of which the other organs showed ample evidence There was no irradiation sclerosis

The contrasting histological patterns in these two cases indicated the dual nature of irradiation damage to the kidneys in man It was the recognition of this which led us to undertake the following experimental investigation

Irradiation of the Kidneys in Rats

METHODS

Experiments were performed with rats of the Wistar strain

All the experiments reported here were on female rats which, at the time of irradiation, were aged 86-97 days, weighed 154-195 g, and had a systolic blood-pressure of 95-130 mm Hg The systolic

IRRADIATION OF KIDNEYS IN RATS (1100r single dose)

—	Experiment 1 (irradiation both kidneys exteriorised)	Experiment 2 (irradiation of one kidney exteriorised)	Experiment 3 (band irradiation of both kidneys in situ)
Number of rats	5	11	12
Highest systolic blood-pressure (mm Hg)	150–220	175–235	155–200 (155–230 after one kidney removed)
Interval from irradiation to hypertension (days)	126–216 (average 155)	152–266 (average 215)	167–287 (average 230)
Controls	Kidneys exteriorised without irradiation (4 rats)	One kidney exteriorised and replaced (6 rats)	Irradiation over chest (5 rats), irradiation of pelvis (3 rats), no irradiation (10 rats)

blood-pressure was measured weekly under light ether anæsthesia by a modification of the tail-plethysmograph method (Byrom and Wilson 1938) The upper limit of normal blood-pressure was taken as 140 mm Hg The rats were maintained on the stock diet and drank tap-water

X rays were from a Victor therapy set working at 200 kV and 10 mA The rays were filtered through 0 5 mm of copper plus 1 mm of aluminium The half-value layer was 1 0 mm of copper Irradiation was applied to the rats by means of special 'Perspex' applicators mounted on a base-plate fixed to the main tube housing after the normal "master-cone" had been removed The focus-skin distance was 16 cm The dose-rate at the applicator face was about 300r per minute with back scatter, and the total dosage in all cases was 1100r[1] at the proximal surface of the kidney, administered at one exposure This dosage was selected after preliminary trials had shown it to be the most consistent in producing hypertension compatible with long survival The dosage assessment, based on suitable ionisation-chamber measurements, was considered accurate to ±5% During exposure the rats were kept under ether/air anæsthesia

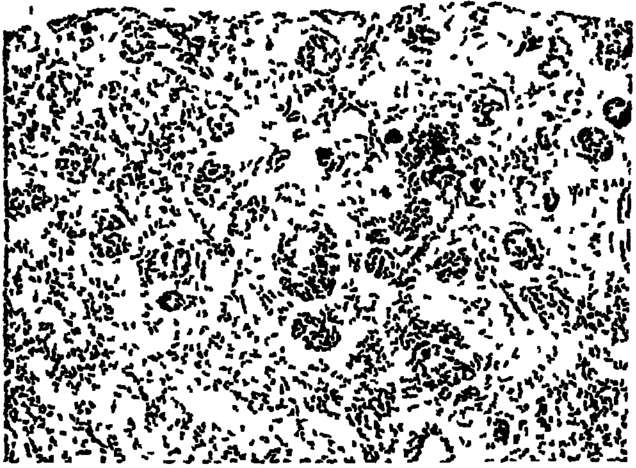

Fig 3—Experiment 1, irradiation of both exteriorised kidneys of rat: irradiation sclerosis with severe fibrinoid necrosis of arteries (Hæmatoxylin and eosin × 58)

Two forms of application were used

(1) The rats were placed prone and a perspex applicator measuring 5 × 3 cm was brought down from above until it was gently pressing on the spine in a transverse direction across the axis of the body Thus a 3 cm band of irradiation could be administered to the rat across the body at any level The upper and lower limits of the kidneys were defined by palpation under anæsthesia and marked on the shaved skin of the back The distance between these limits was less than 3 cm, and the applicator could be so placed that both kidneys received the dosage This form of irradiation we call "band irradiation of kidneys in situ" In control groups the band of irradiation was placed either above the upper or below the lower limits of the kidneys

(2) One or both kidneys were drawn out on to the rat's flank through loin incisions (after freeing the suprarenal gland), and two lead shields with central slots were slipped in opposite directions beneath the kidney with the renal pedicle lying in the slots, thus effectively shielding the rest of the body from irradiation A special perspex applicator, of kidney size and shape, was then brought into contact with the kidney, which was immediately replaced after irradiation This procedure we call "irradiation of the exteriorised kidney"

RESULTS

Experiment 1 Irradiation of Both Kidneys Exteriorised

The details of this experiment are shown in the accompanying table Although only five rats were included in this group, the results were remarkably uniform Hypertension developed in 126–216 days after irradiation (average 155 days), and the range of the maximum blood-pressure was 150–220 mm Hg Controls were provided by repeating the exact operative technique without irradiation, and all these were normotensive at the end of the observation period of 416 days

Pathological findings in kidney (fig 3)—The kidneys were examined after 1–4 weeks' hypertension They were moderately contracted

Histological examination showed severe zonal fibrosis with moderate to severe tubular atrophy Glomeruli in the atrophied areas were crowded together and showed hyaline fibrosis and shrinkage of the glomerular tufts, with slight collagenous thickening of Bowman's capsule In less damaged kidneys many of the glomeruli within the scarred areas appeared relatively normal Outside the areas of fibrosis the renal tissue either appeared normal or showed moderately severe tubular degeneration In both the fibrotic and the non-fibrotic areas of the kidneys acute fibrinoid necroses of glomeruli and arterioles were common

The kidneys of the controls showed no abnormality

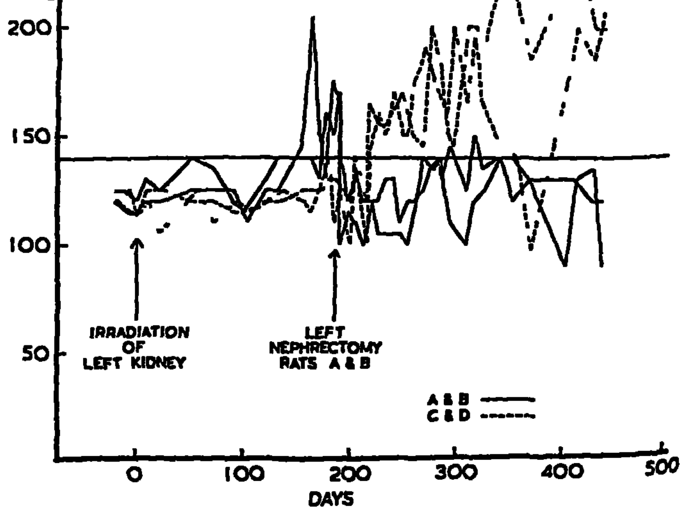

Fig 4—Blood-pressure of rats after irradiation of one kidney, with and without subsequent removal of irradiated kidney

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[1] This dosage was measured before the recent reassessment of the röntgen (Kemp and Hall 1954, Smith 1955) and corresponds to 1175r on the new assessment

Conclusions—Following irradiation of the exteriorised kidneys in the rat, hypertension develops after a latent interval similar to that seen in man. Histologically a picture of irradiation sclerosis is produced which very closely resembles that seen in the human kidney

Experiment 2: One Kidney Exteriorised and Irradiated

Fibrinoid necrosis of arterioles and necrotic lesions in the glomeruli form a fairly constant and prominent feature of irradiation sclerosis Since it has been shown in other experiments, using the technique of renal-artery constriction, that these lesions are secondary to hypertension (Wilson and Byrom 1939), an experiment was devised to see whether this relationship could also be demonstrated in irradiation sclerosis For this purpose it was decided to irradiate one kidney in the hope that a comparison of the vascular lesions in the irradiated kidney with those in the opposite kidney might provide an answer to this problem

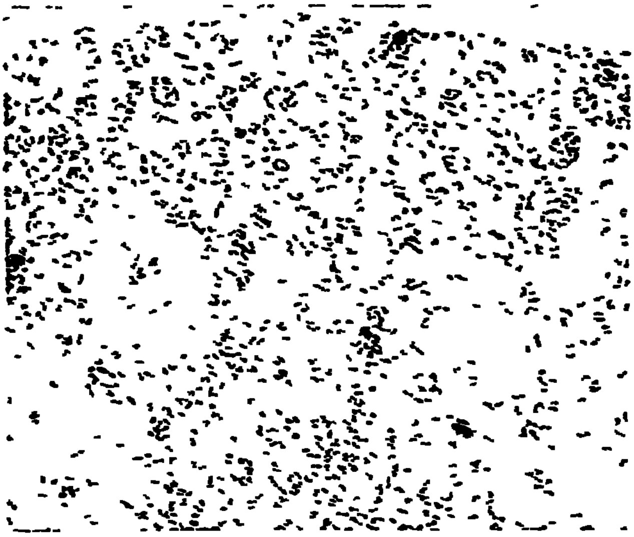

Fig 6—Experiment 2, irradiation of one exteriorised kidney of rat: irradiation sclerosis with severe fibrinoid necrosis involving large and small arteries. (Hæmatoxylin and eosin. × 58.)

The details of this experiment are shown in the table. Eleven rats were included in the series, and in six controls the operative technique was repeated but without irradiation The intervals from irradiation to hypertension were longer than in the first group with limits of 152 to 266 days (average 215 days) The maximum blood-pressure range was 175–235 mm Hg After the blood-pressure rose it remained high, but there were large fluctuations sometimes associated with hypertensive crises In two rats the irradiated kidney was removed shortly after the development of hypertension, and in these the blood-pressure fell promptly and remained normal throughout the observation period. Fig 4 shows this sequence compared with sustained hypertension in two rats in which the irradiated kidney was not removed

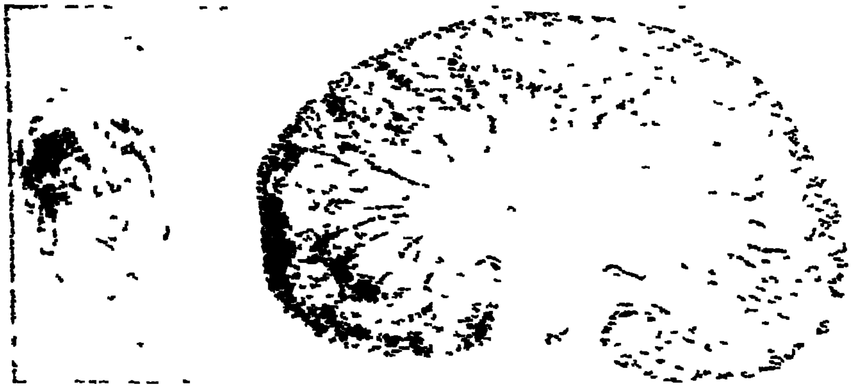

Fig 5—Experiment 2, irradiation of one exteriorised kidney of rat Irradiated kidney contracted, non-irradiated kidney hypertrophied (× 4½)

Pathological Findings in Kidneys—In nine rats of the irradiated group both kidneys were examined histologically after hypertension had been present 14–218 days In contrast with the previous experiment the irradiated kidney was grossly contracted in all the rats and the opposite kidney was considerably enlarged (fig 5)

Microscopically the irradiated kidney showed similar changes to those described in experiment 1, except that fibrosis was much more extensive and severe, and tubular atrophy and regenerative hyperplasia were more marked (fig 6) and in some instances neoplastic changes had developed The opposite (non-irradiated) kidney showed various degrees of acute and organised lesions (fig 7), which included fibrinoid necrosis of arterioles and glomeruli (fig 8), focal tubular dilatation, and hyaline droplet degeneration of the tubular epithelium These changes were identical with those observed in the opposite kidney after unilateral renal-artery constriction (Wilson and Byrom 1939, 1941)

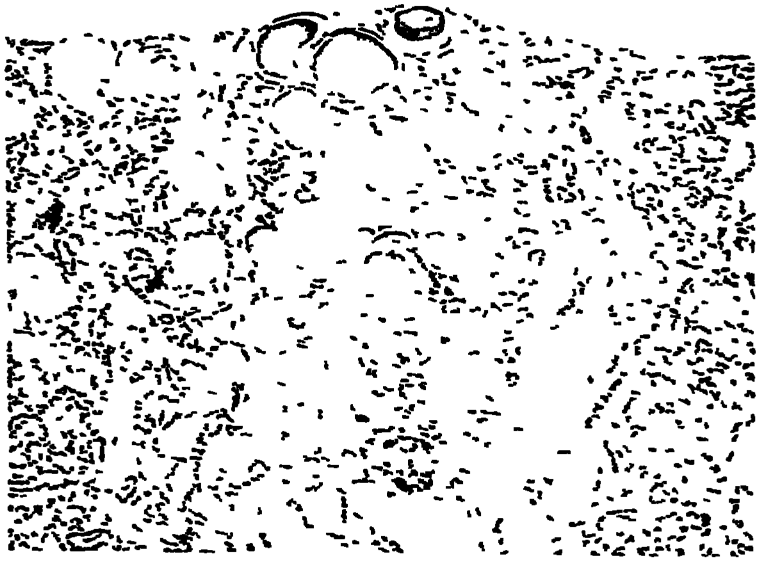

Fig 7—Experiment 2, irradiation of one exteriorised kidney of rat secondary hypertensive damage in opposite (non-irradiated) kidney (Hæmatoxylin and eosin. × 58.)

The extent and severity of the lesions in the non-irradiated kidney were roughly related to the degree and duration of the hypertension. In one rat the blood-pressure remained normal 200 days after irradiation and no lesions were found in the opposite kidney, furthermore fibrinoid arterial necrosis was not seen in the irradiated kidney of this animal although irradiation sclerosis was very severe.

When a comparison was made of fibrinoid arterial lesions in the irradiated and non-irradiated kidneys it was obvious that though similar in nature in the two kidneys, the lesions were of much greater severity in the irradiated kidney, and there was a constant tendency for larger vessels to be affected

In the two members of this series referred to above in which the irradiated kidney was removed as soon as hypertension was noted, examination of the remaining (non-irradiated) kidney showed no lesions in one case and a few scattered healed lesions in the other From a comparison with the non-irradiated kidneys which in other rats had been left in situ and which were exposed to hypertension for various intervals, it seems to be established beyond doubt that the structural changes observed in the opposite kidneys were secondary to the hypertension No lesions were found in the kidneys of the controls, and all the controls were normotensive at the end of the period of observation (430 days)

Comment—This experiment showed that, in the rat as in man, irradiation of one kidney produces irradiation sclerosis and hypertension It is shown that, if the irradiated kidney is removed soon after hypertension develops, the blood-pressure returns to normal If, however, the kidney is not removed and hypertension persists, hypertensive lesions appear in the opposite kidney and rapidly increase in extent In character they resemble the fibrinoid vascular lesions which are present in the irradiated kidney, but in the latter they are more extensive and involve larger arteries Moreover, in one rat the blood-pressure remained normal though interstitial fibrosis was severe, and in this animal fibrinoid vascular lesions were not seen in either the irradiated or the non-irradiated kidney

This experiment therefore provides evidence of two distinct pathological processes, separated in time, which lead to renal structural changes after irradiation—namely, interstitial fibrosis and hypertensive vascular damage Furthermore, from our observations in man it seemed possible that high blood-pressure and the vascular lesions resulting from it might occur independently of the interstitial fibrosis which follows irradiation The next experiment provided additional support for this hypothesis

Experiment 3 Irradiation of Both Kidneys in Situ

To reproduce more closely the conditions in man, the kidneys of the rat were now irradiated without operative interference by " band irradiation in situ " Details of the experiment are shown in the table Twelve rats were irradiated and controls received irradiation of the chest (five rats), or pelvis (three) or no irradiation (ten) Hypertension was noted 167–287 days (average 230 days) after irradiation—i e , somewhat later than in the previous experiments but comparable with the interval observed in man The maximum blood-pressure range was 155–200 mm Hg

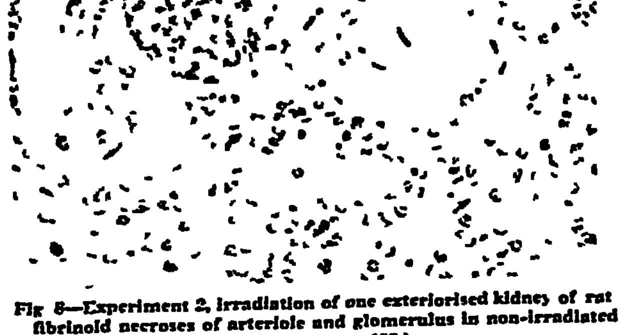

Fig 8—Experiment 2, irradiation of one exteriorised kidney of rat fibrinoid necroses of arteriole and glomerulus in non-irradiated kidney (Hæmatoxylin and eosin. × 185)

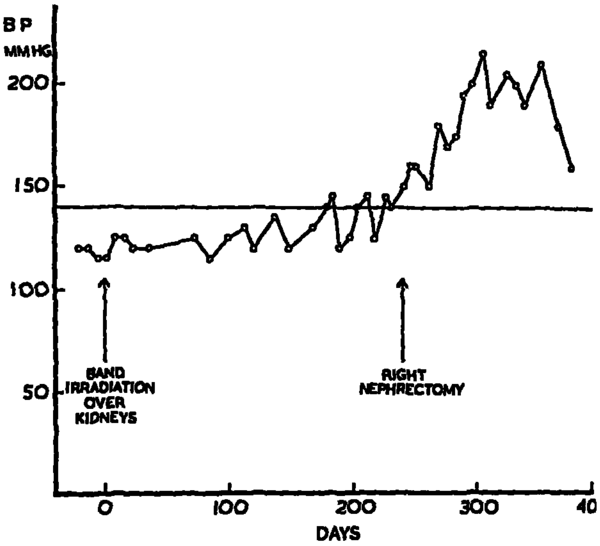

Fig 9—Blood pressure of rat after band irradiation of both kidn in situ

To follow the development of structural changes in t irradiated rats, one kidney was removed when two successi readings at weekly intervals showed a blood-pressure 145 mm or over After this operation the rats survived f periods ranging from 10 to 178 days, during which the ran of maximum blood-pressure was 155–230 mm Hg Fig illustrates a typical example

Pathological findings in kidney—The only changes fou in the *first kidney*, removed as soon as hypertension appeare were scattered focal glomerular and arteriolar necroses Th general architecture of the kidney was unchanged, and in som rats the kidney appeared normal apart from very occasion glomerular lesions (fig 10) The *second kidney* was examin in five cases, the intervals after first nephrectomy being 14, 2 34, 138, and 147 days, the postoperative maximum bloo pressures were 215–230 mm Hg in four of these ra Glomerular and arteriolar lesions with secondary tubul atrophy and focal interstitial fibrosis resembled the appearance in the first kidney but were generally much more extensive and severe and occasionally gave rise to gross disorganisation of the renal pattern These changes are illustrated in figs 11 and 12

A comparison with figs 7 and 8 indicates the remarkable similarity with the hypertensive lesions in the non-irradiated kidney in experiment 2 There was a rough proportionality between the severity of the hypertension before and after the first nephrectomy and the severity of the histological lesions in the two kidneys Thus in one rat in which the highest blood pressure was 160 mm Hg for not more than 10 days before nephrectomy, the first kidney showed minimal lesions In this rat hypertension persisted after nephrectomy for 138 days with a maximum level of 215 mm Hg, and the second kidney showed extremely severe changes

Among the controls, two of the five irradiated over the chest showed an occasional blood-pressure above 140 mm Hg, as did one of the three controls irradiated over the pelvis Scatter of radiation might explain these slight abnormalities In three rats, two of which received irradiation over the chest and one over the pelvis, isolated tubular segments appeared dilated and contained hyaline casts The corresponding glomeruli occasionally showed capsular thickening or adhesions These rats were 18–21 months old and had been normotensive throughout The lesions bore no resemblance to those in hypertensive rats and were not thought to be relevant No lesions were found in other organs in these groups

Of the rats which received no irradiation, all were normotensive throughout the 450 days of observation save one in which two readings were 145 mm Hg The kidneys in this group showed no abnormality

Comment—In this experiment irradiation of the kidneys in situ produced hypertension which was not accompanied by the irradiation sclerosis described in our previous experiments Histological examination of one kidney when the blood-pressure first became high showed slight focal necroses in arterioles and glomeruli—i e , changes which had all the characters of early secondary hypertensive lesions as described by Wilson and Byrom (1939) Longer exposure of the remaining kidney to hypertension led to various grades of renal damage indistinguishable from that found in the non-irradiated kidney when hypertension was produced by irradiation of the contralateral kidney in experiment 2 The renal structural changes observed in this experiment are comparable with those found in some patients who develop malignant hypertension after irradiation of the kidneys, as shown by case 2 (fig 2)

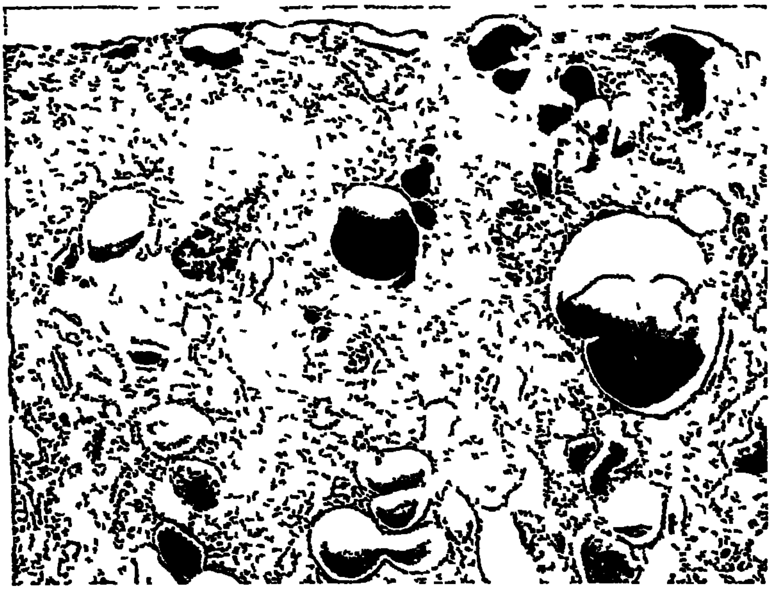

Fig 11—Experiment 3, irradiation of both kidneys of rat in situ structural changes in second kidney exposed to severe hypertension for several months (Hæmatoxylin and eosin × 58)

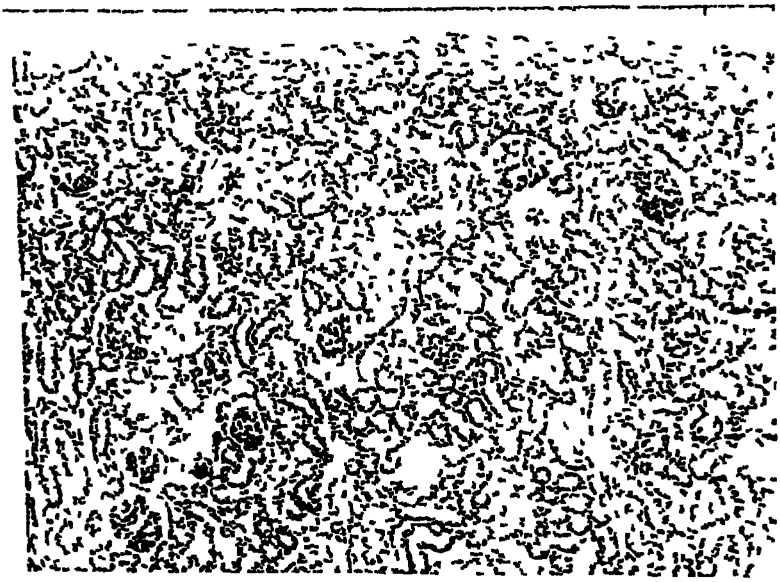

Fig 10—Experiment 3, irradiation of both kidneys of rat in situ normal appearance of first kidney removed at onset of hypertension (Hæmatoxylin and eosin × 58)

We considered the possibility that the rise in blood-pressure might be due either to renal capsular fibrosis or to hilar fibrosis causing compression of the renal artery, but we found no evidence of such lesions, and in no instance did the kidneys show signs of chronic ischæmic atrophy Furthermore, if hypertension were due to constriction of the main renal artery, we might expect, on the basis of the original experiments of Wilson and Byrom (1939), that the kidneys would be "protected" from hypertensive vascular damage

Discussion

From these observations in man and experiments in the rat we are led to conclude that irradiation of the kidneys has two distinct and independent biological effects (1) interstitial fibrosis and (2) hypertension Both in man and in the rat these effects may develop together or separately When they are associated, the structural changes in the kidney present a composite picture of the results of interstitial fibrosis and of hypertensive vascular damage The two effects have different time relations Under the conditions which give rise to interstitial fibrosis this process is far advanced when the blood-pressure first rises Hypertension, on the other hand, takes 4–9 months to develop in the rat, a latent interval similar to that observed in man

In the rat, as in man, there are many parallels between this and other forms of renal hypertension Thus irradiation of one kidney produces hypertension, and removal of the irradiated kidney may bring the blood-pressure back to normal Secondary hypertensive lesions appear in the opposite kidney, and there appears to be a relation between severity of hypertension and extent of these secondary lesions

The most important conclusion from these observations is that, both in man and in the rat, hypertension may be produced by irradiation of the kidney in the absence of the structural changes usually found in

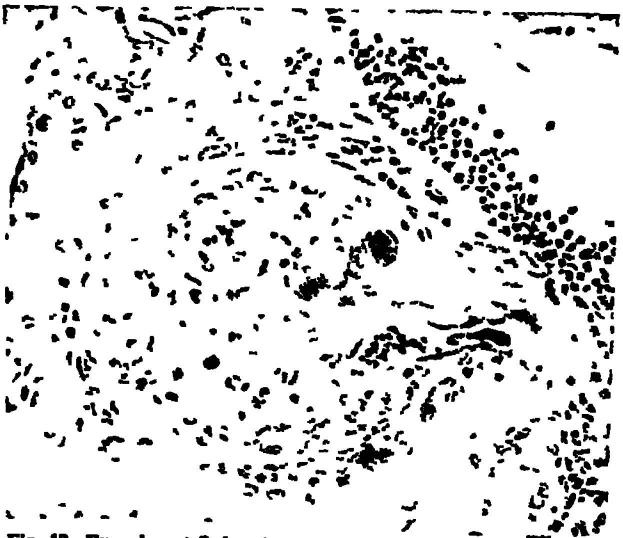

Fig 12—Experiment 3, irradiation of both kidneys of rat in situ fibrinoid necrosis of arteriole and glomerulus in same kidney as in fig 11 (Hæmatoxylin and eosin × 139)

irradiation sclerosis Later, structural changes do occur, but both in man and in the rat they closely resemble the lesions of human essential malignant hypertension, and they must be regarded as secondary to the high blood-pressure These experiments provide evidence, therefore, that renal hypertension can develop without any preceding anatomical lesion, at any rate as revealed by direct microscopy Certainly there are none of the anatomical changes in the kidney which are known to produce high blood-pressure in man or in laboratory animals

Our present experiments do not indicate how renal irradiation produces hypertension, nor do we know what factors determine the development of irradiation sclerosis on the one hand, or hypertension on the other, or indeed the two effects together Further experiments are being made to investigate these problems The latent interval of several months before hypertension appears is a regular and striking phenomenon both in man and in the rat Furthermore, we observed that, in rats which became hypertensive after irradiation of one kidney, fibrinoid necroses of the arteries were more severe in the irradiated than in the non-irradiated kidney and involved larger vessels , this suggests either that hypertension induces more severe lesions in an already damaged kidney (which is not supported by the histological findings in human kidneys when malignant hypertension is superimposed on pre-existing chronic nephritis) or that exposure to irradiation leads to greater vulnerability of the arterial wall In studies on radiation damage to the brain in rabbits (Russell et al 1949) fibrinoid arterial necrosis was found in the area of irradiation Dosage was much larger, and the post-irradiation interval rather shorter, than in our experiments Blood-pressures were not measured, but there is no reason to suspect that hypertension was present These findings suggest that, in the brain, acute arterial damage may result directly from irradiation of high intensity These observations agree with our own in suggesting that irradiation has a definite impact on the vascular system Perhaps the arteries of the kidney are rendered more susceptible to physiological stress, with the result that whatever factors control basal arteriolar tone lead to excessive vasoconstriction The long latent interval between irradiation and hypertension remains unexplained but may be related to the regeneration time of vascular tissue and the selective effect of irradiation on immature cells

The results here presented may have some relevance to the question of a renal mechanism in essential hypertension In his Croonian lectures of 1942, Sir Arthur Ellis said

> "The evidence that essential hypertension is due to primary renal vascular lesions is at present insufficient It is quite possible of course that the mechanism of production of essential hypertension is renal ischæmia, but if this is so it seems more probable that the renal ischæmia is at first functional, being due to some extrarenal factor, and is only later aggravated by renal arteriosclerosis "

Our present clinical and experimental observations seem to us to support the possibility that a functional vascular disturbance of the kidney could be the forerunner of essential hypertension

Summary

Observations in man and experiments in rats are described showing that X-irradiation of the kidneys may produce two biological effects—interstitial fibrosis and hypertension These appear to be independent of on another

Irradiation sclerosis of the kidney is a composite pictur of structural damage due to these separate processes

These observations explain the different histologic changes which may be associated with the syndrome o malignant hypertension, following irradiation of th kidneys in man

Evidence is provided that renal hypertension ma develop in the absence of any recognisable structur lesion

We are indebted to Prof D S Russell and the late Dr G W Boden for helpful discussion We wish also to thank Professo Russell for the necropsy findings, Miss Esme Nichol for technic assistance, and Mr Alan Perry, Lord Evans, and Dr F Ellis for permission to report cases under their care

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PREGNANCY AND COARCTATION OF THE AORTA*

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COARCTATION of the aorta is not uncommon Blackford (1928) estimated its incidence at 1 in 1500 Males predominate over females in a ratio of 3 1 Pritchard's (1953) estimate for females was between 1 in 1000 and 1 in 3000 Whatever the exact figure, one may expect coarctation and pregnancy to coexist occasionally, and the improvement both of diagnosis and of surgical treatment is likely to focus attention more strongly upon management of the pregnancy in such patients Because there is some uncertainty about the influence of pregnancy on coarctation, I have attempted to evaluate the risks

Coarctation Considered Alone

The congestive heart-failure which may occur in infancy (Mustard et al 1955) need not be considered here

MORTALITY

Necropsies have shown that most patients with the "adult" type of coarctation die before the fifth decade of life

74% of Abbott's 200 patients (all of them aged more than 3 years) (Abbott 1928, Hamilton and Abbott 1928) and 61% of 104 patients reported by Reifenstein et al (1947) died before the age of 40

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* Based on a paper read to the symposium on Non-Toxæmic Hypertension in Pregnancy, organised by the Institute of Obstetrics and Gynæcology and held at Hammersmith Hospital, London, on July 4 and 5, 1957

TABLE I—COMPLICATIONS IN 73 CASES OF COARCTATION OF AORTA

Local	Remote
Aneurysm of aorta	Cerebral vascular accidents 4 cases
Dissecting 2 cases	
Non-dissecting 4 cases	
Intercostal aneurysm 10 cases	
Manifest infection or vegetations in the coarctation 10 cases	

Total complications 30 cases (41%)
Associated cardiac lesions aortic-valve disease, 11 cases

Lewis (1933), Bramwell (1947), Campbell and Suzman (1947), Newman (1948), and Shapiro (1949) reported 94 cases of coarctation, of which 27 were fatal The average age at death from cardiovascular causes was 33, and only 7 had passed their 40th year when last seen

CAUSES OF DEATH

The causes of death are documented in the necropsies reported by Abbott (1928) and Reifenstein et al (1947) about 25% of patients died from aortic rupture or aortic dissection, 25% from bacterial endo-aortitis or endocarditis, 25% from congestive heart-failure, about 10% from cerebral vascular accidents, and 15% from other causes The highest average age at death from cardiovascular causes was 39

Campbell and Baylis (1956) reported 16 deaths in 130 patients followed for an average period of five years 7 patients died during or after operation, and the remaining 9 patients did not come to operation 6 of the patients who died were apparently in good health and died suddenly and unexpectedly, mostly in the third decade

Cleland et al (1956) reported 52 patients, of whom 40 came to resection Of the 12 unresected patients 4 died, 2 from heart-failure due to associated valvular lesions, 1 from subarachnoid hæmorrhage, and 1 from dissection of the aorta Since that paper was published, Mr Cleland has treated a further 21 cases by resection The complications in the total series of 73 patients are listed in table I Of the 61 resected patients 6 died, 5 of them from local complications (1 did not come to necropsy) Of the 30 patients with complications (whether lethal or not) 26 had complications which involved the aorta and the region of the coarctation

Local complications are common and hazardous, the more so because many are silent, and sudden death and a shortened life-span are distressingly frequent in coarctation, irrespective of pregnancy

ASSOCIATED CARDIAC LESIONS AND HEART-FAILURE

Any attempt to assess the hazards of coarctation must take into account the presence of added cardiovascular lesions

A bicuspid aortic valve was found in about 20% of necropsies by Abbott (1928) and in about 40% by Reifenstein et al (1947) Aortic regurgitation was present in nearly 25% of the 130 cases of Campbell and Baylis (1956) and tended to become more serious with increasing age Aortic-valve stenosis was present in 11% of Reifenstein et al 's series, and in 6 of Campbell and Baylis' patients Aortic-valve disease was present in 11 of the 73 cases in our own series

Mitral-valve disease, ventricular septal defect, and patency of the ductus arteriosus are less common

Cardiac lesions confer the added hazards of bacterial infection and heart-failure Cleland et al (1956) found heart-failure only in patients with severe valvular lesions 18 of 19 patients (Reifenstein et al 1947) and 7 of 8 patients (Campbell and Baylis 1956) who died of congestive heart-failure had additional cardiac disease Campbell and Baylis (1956) find that aortic regurgitation with coarctation may lead to heart-failure in the third decade, and they point out that infective endocarditis may accelerate such failure

HYPERTENSION

Hypertension is rarely severe, and, although systolic pressure may sometimes be high, the pressure is extremely labile Important hypertensive cardiovascular disease occurs only as an extreme rarity (Cleland et al 1956) Hypertension may, however, contribute to cerebral vascular catastrophes, and there is some direct relation between intracranial hæmorrhage and the level of the blood-pressure (Reifenstein et al 1947, Campbell and Baylis 1956) Moreover patients with coarctation tend to have congenital intracranial " berry " aneurysms

SURGERY

Resection of the coarctation, with or without the use of a graft, is now an established procedure The mortality is now 5–10%—usually 5% in cases without complications (Campbell and Baylis 1956) Gross (1953) reported only 2 deaths in his last 100 cases In our series (Cleland et al 1956), there were 6 deaths in 61 resected cases, including cases complicated by aortic aneurysm Resection lowers the blood-pressure (Gross 1953, Counihan 1956, Cleland et al 1956, Campbell and Baylis 1956)

Coarctation with Pregnancy

123 cases of coarctation and pregnancy have been published

Benham (1949) collected 53 cases from the literature, and Rosenthal (1955) collected 38 more published subsequently and added 5 cases of his own Porter (1955) added 1 case, Dixon and Hartley (1955) 2 cases, Gropper and Schroeder (1956) 1 case, and Espino Vela and De Castro Abreu (1956) 6 cases Campbell and Baylis (1956) mention 2 cases in their review of 130 patients with coarctation Halonen et al (1956) have published 15 more cases

To these may be added 13 cases of my own, including the 10 described by Cleland et al (1956) There is thus a grand total of 136 cases

MORTALITY

The mortality of pregnancy complicated by coarctation is 9 5% (13 cases) This mortality is in striking contrast to that of 29% in the combined series of 94 cases described by Lewis (1933), Bramwell (1947), Campbell and Suzman (1947), Newman (1948), and Shapiro (1949), and less than that of 12 3% in the 130 cases published by Campbell and Baylis (1956) The ages at death are not comparable in the different series but the average age at death in the combined series of 94 cases was 33 More-

TABLE II—PREGNANCY AND COARCTATION OF AORTA

Cases published by other workers	123
Personal cases	13
Total	136
Mortality connected with pregnancy	13 cases (9 5%)
Cause of death in 13 fatal cases	
Rupture of aorta	3 cases
Rupture of dissecting aneurysm	3 cases
Cerebral vascular accident	2 cases
Infective endocarditis on aortic valve	1 case
Unknown	1 case
Congestive heart-failure	2 cases
Pulmonary œdema	1 case
	13
Associated cardiac defects in 13 fatal cases	8 cases

(The 2 patients who died of congestive heart failure and the 1 who died of infective endocarditis had cardiac lesions in addition to coarctation)

Mortality related to total pregnancies 13 cases in 354 pregnancies (3 4%)

over, 7 of the patients of Campbell and Baylis (1956) died after operation and therefore cannot strictly be admitted to the analysis Nevertheless, the mortality-rate of coarctation in pregnancy probably does not exceed that of coarctation alone (table II)

In assessing the hazards of pregnancy it is important to know also the mortality-rate in terms of the total number of pregnancies There were 13 deaths in 354 pregnancies (mortality 3 7%) Many patients had multiple pregnancies without mishap, but it must be admitted that 7 of the 13 *patients died in their first pregnancy* *Of the remaining 6* patients, 2 died in their second pregnancy and 1 each in the third, fifth, sixth, and ninth pregnancies None of our 13 patients died (table III)

TABLE III—PERSONAL SERIES OF PATIENTS WITH PREGNANCY AND COARCTATION OF AORTA

Patients pregnant	13
Deaths	0
Patients with multiple pregnancies	12
Patients resected	10
Patients pregnant before resection	9
Patients pregnant after resection	2
Pregnancy terminated (2nd pregnancy, for aortic incompetence)	1

CAUSES OF DEATH

The normal hazards of coarctation are to be expected in addition to those of pregnancy The causes of death are listed in table II, which shows that the two commonest single causes were aortic rupture and aortic aneurysm As in previously published series, heart-failure was *found only when cardiac lesions were present* There were 3 such cases 2 of congestive heart-failure and 1 of pulmonary œdema In patients without cardiac lesions the deaths were due to rupture of the aorta and cerebral vascular accidents

Let us now consider whether pregnancy predisposes to these hazards of coarctation

Rupture of the Aorta

Aneurysm and aortic rupture are almost always due to medial necrosis of the aorta, but occasionally to infective endocarditis (Campbell and Baylis 1956) A rise in blood-pressure might predispose to rupture, but, as Reifenstein et al (1947) pointed out, the blood pressure is not especially high in those cases in which aortic rupture occurs Wide fluctuations in blood-pressure have been suggested as a precipitating cause of dissection in patients with *malignant hypertension* receiving hypotensive drugs (Beaven and Murphy 1956), and the blood-pressure is notably labile in coarctation, though probably not more so during pregnancy (Dixon and Hartley 1955) Other factors in pregnancy have also been suggested—e g, thyroid deficiency (Joule 1949) and hyperlipæmia (Schnitker and Bayer 1944)

Schnitker and Bayer (1944) reported that 24 of 49 females dying from dissecting aneurysm of the aorta (without coarctation) were, or had recently been, pregnant No proof, however, of the significance of any of these factors is forthcoming, and most authors have emphasised the importance of a rise in blood-pressure in pregnancy and labour causing the aortic wall to burst

Infection at the site of the *coarctation may lead* to an aneurysm, as in 1 of our patients Moreover vegetations may remain unsuspected upon the coarctation for a long time (Cleland *et al* 1956) and might cause serious disruption of the aortic wall before detection It is not known, however, whether pregnancy predisposes to such infection

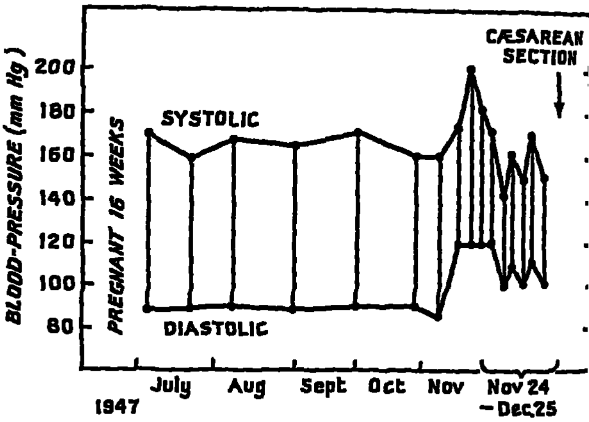

Fig 1—Blood-pressure during first pregnancy of a patient age 23 years with coarctation of the aorta

Hypertension in Pregnancy

It has been often assumed that, in coarctation, th blood-pressure rises in pregnancy and labour If it does the risks of aortic rupture and intracranial aneurysm ma certainly be increased, but Dixon and Hartley (1955 found, with coarctation, in 2 pregnant patients that th blood-pressure behaved as in normal pregnancy, fallin in the middle trimester and rising towards the end o pregnancy, except that the rise was not so high as it may b in the later months of normal pregnancy in the thre labours studied the blood-pressure did not rise appreciabl *above its upper level before pregnancy* Pritchard (1953 found the same in 2 pregnancies and labours

In two pregnancies in 1 of our patients the blood pressure showed the same tendency as that reported b Dixon and Hartley (1955)

The patient, aged 23, was first seen when sixteen week pregnant with *her* first child Her blood-pressure remaine stable throughout the greater part of pregnancy, the diastoli pressure remaining below 90 mm Hg It rose temporaril to 200/*115* mm *Hg shortly* before term but fell again befor cæsarean section was done (fig 1) In her second pregnanc her blood-pressure fell steadily and gradually and did not ris before term (fig *2*) *Two years later her systolic pressure* wa higher than at any time during her pregnancies except fo the temporary rise before her first cæsarean section

At no time in either pregnancy was her systolic pressur higher than was usual for her when not pregnant

These observations, the absence of evidence suggesting a tendency to medial necrosis of the aorta in pregnancy, and the similarity of the mortality-rates of coarctation with and without pregnancy suggest that pregnancy does not

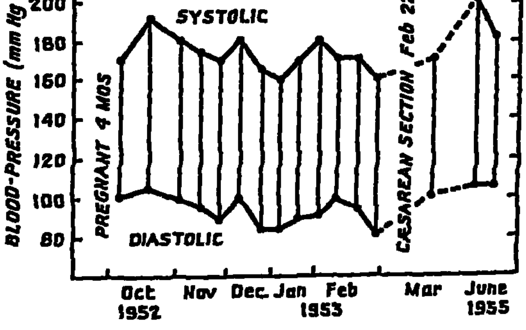

Fig 2—Blood-pressures during and after second pregnancy of same patient as in fig 1

confer an added risk to patients with uncomplicated coarctation.

Coarctation Complicated by Heart-disease

The presence of added heart-disease may radically alter the picture of coarctation, because the hazards of heart-failure and bacterial endocarditis are added. The rarity of heart-failure in adults in the absence of cardiac lesions indicates the importance of heart-disease. In pregnancy cardiac lesions assume an even greater importance. Of the 13 patients who died 8 had cardiac lesions, 3 of these died from heart-failure and 1 from infective endocarditis on an abnormal aortic valve. Appreciable valvular lesions are likely to increase in severity with the years, notably aortic regurgitation (Campbell and Baylis 1956).

It is not possible accurately to compare the risks of coarctation with added cardiac disease in the pregnant and in the non-pregnant, but it seems reasonable to suppose that the risks are likely to be greater in pregnancy. Certainly the hazard of heart-failure, which is most unusual in uncomplicated cases, is added to those of aortic rupture, infection, and cerebral vascular accident.

Of our own series of 13 pregnant patients, only 1 had important associated valvular disease—namely, aortic incompetence. For this reason her second pregnancy was terminated in the third month, and subsequently the coarctation was resected.

Management of Pregnancy

Views on management have varied widely.

Mendelson (1940) advised therapeutic abortion early in pregnancy and cæsarean section and sterilisation at term if the pregnancy is far advanced when the coarctation is detected.

Benham (1949) advised cæsarean section at term to avoid an increase in blood-pressure during vaginal delivery.

Pritchard (1953), however, analysed the maternal fatality-rate in the light of the type of delivery and found that it was almost identical in both cæsarean section and vaginal delivery (7·1% for cæsarean, 6·5% for vaginal). He advised vaginal delivery with a short second stage.

Dixon and Hartley (1955), in the light of their observations on the blood-pressure during delivery, were of the same opinion.

All writers lay stress on careful antenatal supervision, adequate rest if cardiac symptoms supervene, and prophylaxis against bacterial infection. No attempt has previously been made, however, to separate patients with important cardiac lesions from those without, and this point seems to be fundamental to the understanding of correct management.

COARCTATION WITHOUT ADDED HEART-DISEASE

It is now our view (Cleland et al. 1956) and that of others (Gross 1953, Campbell and Baylis 1956) that resection should be undertaken prophylactically in young persons. Early recognition and surgical correction of coarctation should therefore in the future reduce the problems of the management of pregnancy. Nevertheless patients with unrelieved coarctation will continue to become pregnant. It is doubtful, from published and personal experience, whether the hazards of uncomplicated coarctation are really increased by pregnancy, and it can be argued that the risks run in pregnancy are not greater than in the non-pregnant state, especially as the blood-pressure tends to fall rather than to rise during pregnancy and normal labour.

I therefore suggest that patients with uncomplicated coarctation should be allowed to go to term, and be delivered by the vaginal route, with a shortened second stage. Very careful watch must be kept during pregnancy for signs of aortic infection and of aortic aneurysm. Any increase in size of the aorta, unexplained pain in the chest or back, or pyrexia, will indicate the necessity for further investigation, including blood-cultures, so that, if an aortic aneurysm threatens to form, resection can be advised. Successful resection during pregnancy has been reported by Peterson et al. (1953), Miller and Falor (1952), and Tebow et al. (1954).

If resection is not required during pregnancy it should be advised at a suitable time after delivery. After resection further pregnancies can probably be contemplated without anxiety. Miller and Falor (1952) and Pritchard (1953) reported successful pregnancies after resection of coarctation, and 2 of our 13 patients were delivered successfully after resection.

If infective endocarditis occurs during pregnancy, a full course of chemotherapy, followed by resection, is indicated. If the pregnancy is less than twenty weeks old, termination may be advisable, but each case must be judged on its own merits. If an aortic aneurysm is suspected, resection should be done at once under full chemotherapy.

COARCTATION WITH HEART-DISEASE

When serious heart-disease is present—and especially if there is appreciable cardiac enlargement, which is very unusual in uncomplicated coarctation—a much more serious view must be taken. It is of the greatest importance to make the diagnosis early, so that the pregnancy can be terminated before the twentieth week. If the pregnancy has progressed further, the management should be that of any patient with heart-disease in pregnancy, except that resection of the coarctation may still be considered.

Considerable difficulty may be experienced in diagnosing slight degrees of aortic-valve stenosis due to a bicuspid aortic valve, since ejection systolic murmurs are invariably present in coarctation, may be exaggerated in pregnancy, and may closely resemble those of aortic stenosis. However, slight degrees of aortic stenosis are probably not important hæmodynamically, although they constitute an added hazard from infection. These difficulties underline the importance of very careful cardiological assessment early in pregnancy, and of consultation between cardiologist and obstetrician to plan management of the pregnancy and delivery.

It is not necessarily true that all cases have “ at least moderate cardiac disease ” (Pritchard 1953). Patients who have reputedly developed heart-failure in pregnancy have probably had appreciable disease of the aortic valve or other cardiac lesions previously unsuspected.

If pregnancy must be terminated because of added cardiac disease, sterilisation should not be carried out unless it is certain that neither the cardiac lesion nor the coarctation is amenable to future surgical correction.

Summary

The hazards of coarctation and the results of surgical treatment are briefly reviewed. The added risks of pregnancy are assessed in the light of personal experience and that of other workers. The behaviour of the blood-pressure during pregnancy in patients with coarctation is discussed.

Pregnancy is not necessarily an added hazard to the patient with coarctation, provided that complications are not present and that serious cardiac disease does not coexist.

It is suggested that pregnancy be allowed to continue in uncomplicated cases, very careful watch being kept for the onset of complications at the site of the coarctation, which would indicate the need for resection during pregnancy

In cases with appreciable heart-disease the pregnancy should be terminated at an early stage

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MANIPULATION IN THE MANAGEMENT OF CHRONIC LOW BACKACHE DUE TO "LUMBOSACRAL STRAIN"

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A REVIEW of cases of chronic low backache seen in the orthopædic department of the Middlesex Hospital in recent years has shown that a very high proportion have been classified as "lumbosacral strain"

The term "lumbosacral strain" is not an ideal one, but in our present state of ignorance regarding the exact pathology of such cases it is concise and useful for classification The general pathological concept is that of a chronic localised disc degeneration, usually at the L5–S1 level, with associated derangement of the corresponding posterior joints and ligaments, from which pain presumably arises

In the early stages of the lesion the condition of the posterior joints is essentially a subluxation or "instability", with associated ligamentous strain, but in the later stages a true osteoarthritis, the outcome of long-standing mechanical derangement, develops and can be clearly demonstrated by oblique radiographs of the lumbosacral spine

The ætiology may well vary from case to case In some there seems to be an insidious primary degeneration of the disc, whereas in others a traumatic incident may be the cause of the damage (Newman 1952) However that may be, these cases form a fairly typical clinical group of large dimensions Cases presenting evidence of nerve-root involvement or of generalised lumbar spondylosis are excluded from this group

It is our belief that, in the great majority of such patients excluding the very few in whom symptoms are sufficiently disabling to warrant consideration of lumbosacral fusion, the long-term management lies in teaching them to "live with their back," with suitable adjustment of activities and posture With an intelligent patient, reassurance and advice along these lines may be all that is required, but the average hospital patient, sent for the advice of a "specialist", expects something more positive in the way of treatment

Of the many forms of active palliative treatment possible, "manipulation" is undoubtedly the most convincing to the patient Indeed, if it is not offered many will subsequently seek advice elsewhere In view, however, of the numbers involved and the fact that we are dealing with what is usually no more than a "nuisance disease", any hospital treatment should be as far as possible "definitive", so that clinic and physiotherapy department do not become inundated with these cases

The object of this investigation was an essentially practical one—to discover whether manipulation of the lumbar spine under general anæsthesia gives a sufficiently high proportion of immediate satisfactory results in this type of case to justify its routine use, with the narrow twin objectives of giving the patient a "good start" in carrying out the general regime suggested above and of providing an avenue of early disposal of these cases from the orthopædic clinic as "satisfied customers"

Clinical Material

The early results of manipulation in 250 consecutive cases diagnosed as lumbosacral strain, in which manipulation was done as the primary treatment, were analysed There were 84 males (average age 39) and 166 females (average age 36) of whom 116 were married and 50 single

Routine Management

"Orthopædic" manipulation of the lumbar spine was done under general anæsthesia with complete relaxation This was followed by an average period of two weeks' physiotherapy, to instruct the patient in simple spinal exercises and in correct posture and techniques of lifting and bending All the patients were treated as outpatients

Assessment of Results

Physical signs are few or absent, and therefore assessment must be largely subjective The following classification was used, based essentially on the patient's own report at the first visit following treatment

Group I, "*cured*" complete dramatic relief of all back symptoms

Group II, "*improved*"

(1) Much improved, to a degree where the patient felt that no further active treatment was required, although some residual symptoms persisted

(2) Some improvement, but symptoms *still present* which the patient considered significant, progressing to group (1) after further physiotherapy

(3) As in group (2) but adequate comfort attained only by wearing a lumbosacral corset

Group III, "*no change*'

(1) Not helped by manipulation or any further treatment

(2) Subsequently reporting benefit from the provision of a lumbosacral corset

Group IV, "*worse*'

(1) Made worse by manipulation and not helped by any further treatment

(2) Subsequently reporting benefit from the provision of a lumbosacral corset

The results obtained were as follows

Group	*No of cases*	
I	25 (10 0%)	(86 8%)
II (1)	136 (54·4%)	
II (2)	20 (8 0%)	
II (3)	36 (14·4%)	
III (1)	6 (2·4%)	(13 2%)
III (2)	18 (7 2%)	
IV (1)	4 (1 6%)	
IV (2)	5 (2·0%)	

Discussion

Although the primary aim was to assess the practical value of manipulation in the management of "lumbosacral strain", the composition of the group of 250 cases studied is of some interest. The ratio (1 to 1 8) of males to females confirms the clinical impression that this type of backache is more common in females than in males Were externally applied strain an important ætiological factor, one would expect the condition to be more common in males

Two possible predisposing factors in the female immediately come to mind the greater lumbosacral angle, which would increase the shearing strain on this region, and the possible effects of pregnancy and childbearing The latter possibility has not been studied in detail, but the ratio of 2 3 to 1 of married to single women does not suggest that childbearing has been an important ætiological factor in this series, in view of the normal ratio of married to single women in the age-group under consideration

There is no more controversial treatment in the management of backache than "manipulation" Opinions vary sharply from those of the "osteopathically" inclined, who would have us believe that virtually all backache can be cured with certainty by manipulation, often involving very specialised manœuvres, to those who hold that manipulation has no place in the reputable management of backache in orthopædic practice The latter are wont to attribute any success of the former to psychological influences Although this possibility cannot be completely ruled out, the patients in this series were not subjected to any psychological pressure In other words, no effort has been made to "sell" manipulation as a certain cure for all their ills Manipulation was done by different operators working on anæsthetised patients The technique of manipulation was that of general orthopædic manipulation of the lumbar spine, aiming to put the lumbar spine through a complete range of movement It is therefore reasonable to assume that the results obtained are in some way due to the physical manœuvre of manipulation and therefore capable of general repetition

Although only 10% of the patients were dramatically "cured", it was possible to discharge 64 4% (group I plus group IIa) at the first clinic visit after manipulation as "satisfied customers" In this group both our objectives have been achieved A further 22 4%, however, reported some improvement, hence manipulation was worth while from the patient's point of view in 86 8% of cases In only 3 6% was any harm done, inasmuch as the patient felt worse after the manipulation, and in 9 6% the manœuvre was a waste of time for all concerned

23% of the patients were ultimately fitted with a lumbosacral corset, and it might well be argued that this might have been more expeditiously applied as the primary management Unfortunately a review of the material has not revealed any common factor which might be assessed before manipulation to forecast the likely result The ratio of males to females in all groups closely paralleled the ratios of the totals The state of the pathological process, judged clinically and radiographically, did not prove any guide to the likely subjective improvement following manipulation, nor did any particular age-group respond especially well

We may conclude that manipulation of the lumbar spine under general anæsthesia, although entirely empirical, produced results in this group of patients which go far towards fulfilling the aims set out above for the active palliative treatment of "lumbosacral strain" in hospital practice Manipulation provides one satisfactory practical means of managing this ever-present problem in the orthopædic clinic

Summary

Long-term relief in cases of "lumbosacral strain" depends mainly on the patient's ability to adjust posture and activities to the limitations of the spine

Manipulation under general anæsthesia gives a sufficiently high proportion of immediate satisfactory results to justify its routine use as a palliative measure in the hospital management of such cases

I wish to thank Mr Philip Wiles and Mr Philip Newman, under whose care these patients were, for permission to publish this material and for help and advice in the preparation of this paper

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SURGERY DURING LONG-TERM TREATMENT WITH ADRENOCORTICAL HORMONES

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Although the place of the adrenocortical hormones in the treatment of rheumatoid arthritis remains controversial, they are now often used in the long-term management of this and other diseases It is inevitable that, on occasion during such treatment, indications will arise for surgical treatment of the primary or some intercurrent disease There still appears to be a widespread belief that administration of adrenocortical hormones adversely affects healing and resistance to infection It is the experience of this unit, however, that the administration of moderate doses of these hormones adds no danger to the operation concerned and carries no additional risk of complications Our findings agree with many recent reports that most surgical wounds heal normally during continuous treatment with adrenocortical hormones

Material

We have records of 19 patients who have undergone thirty-six surgical operations while under treatment with adrenocortical hormones We are not concerned here with the indications for treatment with these hormones or with side-effects other than those bearing on the response to surgery The accompanying table gives the details The cases are divided into groups according to whether the operation was elective or emergency, and clean or septic Since 9 of the 19 patients had more than one operation, we have numbered both the patients and their operations

All the patients had chronic rheumatoid arthritis except case 2 (ankylosing spondylitis), case 3 (disseminated lupus erythematosus), case 18 (polyarteritis nodosa), and case 12 (breast cancer)

Dosage

Immediately before operation all the patients were receiving oral cortisone or an analogue or corticotrophin sufficient to suppress at least partly the symptoms of their disease The preparations given are listed in the table in the order in which they were used, the one being taken at the time of operation being the last mentioned Steroid therapy was continued over the period of operation in all but 1 case, and it has been our routine to give additional cortisone to patients receiving this drug or an analogue The table shows that most of the operations for which no additional cortisone was given were minor The precise schedule of this additional dosage varied somewhat, usually, for operations not involving the gastro-intestinal tract, 75–100 mg of cortisone acetate was given intramuscularly twenty-four hours and one hour preoperatively, or a single injection of 150 mg an hour preoperatively, oral administration being continued until the time of operation and resumed as soon as possible afterwards For partial gastrectomy 100–150 mg of cortisone was given intramuscularly twenty-four hours and one hour preoperatively and a further 100 mg twelve hours postoperatively intramuscular administration was continued for the next three days, with a daily dosage of 100, 100, and 75 mg, and oral administration was resumed on the fourth postoperative day

No dosage has been listed for the 7 patients receiving corticotrophin, because the variation in strength between the batches of corticotrophin at present available and the individual variation in responsiveness make the nominal dosage meaningless All these patients, however, showed clinical evidence of suppression of their disease, and all 5 patients in whom the urinary excretion of 17-hydroxy corticosteroids (Appleby et al 1955) was estimated showed evidence of adrenal stimulation, corticotrophin was continued over the operation, but no additional dose was given The management of patients receiving corticotrophin is discussed below

Complications

In twenty-six of the thirty-six operations the postoperative course and wound healing were normal Cases 5, 6 (operation 1), and 8 (operation 2) developed slight superficial wound infections, which responded rapidly to treatment and did not significantly affect healing, and case 9 had a hæmatoma

Serious complications occurred in cases 3, 13, and 14 (see below)

Discussion

Side-effects

Some of the earlier published reports (Ragan et al 1949, Baker and Whitaker 1950, Baxter et al 1951) emphasised the possibility of side-effects of corticosteroid therapy Among these several are important in surgery, notably defective healing of wounds and bone, impaired resistance to infection, modification of the clinical picture of the acute surgical condition, and suppression of normal pituitary-adrenal responses

These reports were based on experiments on animals given a relatively large dosage They have undoubtedly

OPERATIONS UNDER TREATMENT WITH ADRENOCORTICAL HORMONES

Case no	Operation no	Sex	Age (yr)	Nature of operation	Form and duration of steroid therapy before operation	Daily † dosage at time of operation (mg)	Additional hormone over operation	Operative or postoperative complications
Elective clean operations								
1	1	M	38	Excision of nodule from knee-joint	Cortisone 11 mos	75 0	Yes	Nil
	2			Excision of nodule from knee-joint	,, 12 mos	75 0	Yes	Nil
	4			Gastrojejunostomy	,, 30 mos	50 0	Yes	Nil
2	1	M	47	Cup arthroplasty of hip	,, 20 mos	75 0	Yes	Nil
	2			Cup arthroplasty of hip	,, 22 mos	75 0	Yes	Nil
3	1	F	55	Pinning of fractured neck of femur	Corticotrophin 8 mos	†	†	Non-union
	2			Removal of pin	,, 11 mos	†	†	Delayed healing of wound
	3			Excision of head of femur	,, 11 mos Prednisone 2 mos	15 0	Yes	Delayed healing (anæmia)
4	1	F	32	Arthrodesis of wrist	Cortisone 19 mos	75 0	No	Nil
	2			Excision of head of radius	,, 31 mos	75 0	Yes	Nil
	3			Arthrodesis of wrist	,, 41 mos	62 5	Yes	Nil
5		F	37	Bilateral hallux valgus operation	,, 42 mos	62 5	Yes	Small stitch abscess
6	1	F	58	Partial gastrectomy	,, 30 mos Hydrocortisone 4 mos	70 0	Yes	Slight superficial wound infection
	2			Arthrodesis of knee	Cortisone 30 mos Hydrocortisone 30 mos	75 0	Yes	Nil
7	1	F	48	Excision of encysted hæmatoma of calf	,, 20 mos	60 0	No	Nil
	2			Excision of encysted hæmatoma of calf	,, 32 mos Prednisone 14 mos	20-0	Yes	Nil
8	1	F	45	Dilatation and curettage	Cortisone 6 mos	62 5	Yes	Nil
	2			Hysterectomy	,, 6 mos Hydrocortisone 5 mos	60 0	Yes	Slight superficial wound infection
9		F	55	Laparotomy for adenocarcinoma of ovary	Cortisone 15 mos Corticotrophin 15 mos	†	†	Hæmatoma of wound
10		F	42	Cæsarean section	,, 37 mos	†	†	Nil
11	2	F	43	Partial gastrectomy	Prednisone 19 mos	20 0	Yes	Nil
12		F	41	Simple mastectomy	Prednisolone 3 mos	17 5	No	Nil
Emergency clean operations								
1	3	M	38	Suture of perforated duodenal ulcer	Cortisone 15 mos*	75 0	No*	Nil
6	3	F	58	Strangulated femoral hernia	,, 2 wks	75 0	No	Nil
8	3	F	45	Partial gastrectomy for hæmatemesis	,, 6 mos Hydrocortisone 6 mos	60 0	Yes	Nil
11	1	F	43	Suture of perforated gastric ulcer	Prednisone 15 mos	20·0	Yes	Nil
13		M	35	Partial gastrectomy for hæmatemesis	Cortisone 34 mos Hydrocortisone 14 mos	60·0	Yes	Died 24 hr post-op
14	1	M	46	Partial gastrectomy for hæmatemesis	Corticotrophin 48 mos	†	†	*Burst abdomen*
	2			Reclosure of wound	,, 48 mos	†	†	Died 24 hr post-op
15		M	53	Suture of perforated gastric ulcer	,, 47 mos	†	†	Nil
16		M	55	Strangulated inguinal hernia	Cortisone 18 mos	75 0	No	Nil
Elective septic operations								
17		M	42	Antrostomy	Corticotrophin 18 mos	†	†	Nil
18		M	48	Mastoidectomy	Cortisone 30 mos Prednisone 7 mos	25 0	Yes	Nil
11	3	F	43	Multiple dental extractions	,, 11 mos	20·0	No	Nil
	4			Multiple dental extractions	,, 11 mos	20·0	No	Nil
Emergency septic operation								
19		F	37	Drainage of orbital abscess	Corticotrophin 10 mos	†	†	Nil

* Cortisone was stopped on day of operation and for several weeks afterwards

† For dosage in cases treated with corticotrophin see text

influenced the attitude of many surgeons towards operating during treatment with adrenocortical hormones, although it was also shown that, if doses of the order usually given therapeutically were administered to animals, there was little evidence of these side-effects (Cole et al 1951) Some aspects of our own experience are discussed here in the light of these experimental findings

Healing

Thorn et al (1954) state that serious interference with wound healing is rare unless the dosage is large (more than 150 mg of cortisone daily) and prolonged and protein intake inadequate

Wound healing was normal in 17 of our 19 patients , the 2 exceptions were receiving corticotrophin and showed evidence of excessive adrenal stimulation at the time of operation

Case 3 —At the time of her first operation for pinning of spontaneously fractured neck of femur the patient presented many of the features of Cushing's syndrome, and her daily excretion of 17-hydroxycorticosteroids was high , in spite of this her wound healed normally, although the fracture did not unite When the pin was removed nine weeks later, she showed less evidence of hyperadrenalism, but wound healing was delayed Healing was again delayed after her third operation, when prednisolone 15 mg daily had been substituted for the corticotrophin, but she was found to be anæmic, and, once the anæmia had been corrected, healing was rapid , the slow healing after the second operation was also probably due partly to anæmia

Case 14 had a burst abdomen four days after partial gastrectomy His mean urinary excretion of 17-hydroxycorticosteroids over this period was 40 mg daily, and it is therefore likely that the defective wound healing was related to the excessive production of corticosteroids

Operations on bone were followed by normal healing in all except case 3 Three arthrodeses and a bilateral cup arthroplasty of the hip-joints were completely successful, and clinical and radiological evidence of sound union was obtained within the expected time

Individual variation in susceptibility to the various effects of the hormones appears to be considerable One can judge more accurately whether healing is likely to be delayed by inspection of the patient than by consideration of the dosage of hormones given This clinical approach can be reduced to simple terms

(1) Patients who appear normal will heal normally

(2) Patients who show the features of Cushing's syndrome may heal badly

(3) Patients who have definite rounding of the face but only slight other side-effects will probably heal normally, unless

(4) they also have anæmia, severe wasting, or gross abnormality of the plasma-protein levels, when they may heal badly

Surgery in Peptic Ulceration

It is generally agreed that the incidence of peptic ulcers increases in patients receiving adrenocortical hormones orally, and that the risks of perforation and of hæmorrhage are also somewhat increased However, it has been reported that ulcers healed with medical treatment although the administration of adrenocortical hormones was continued (Bollet et al 1955), and we also have observed this

In our experience surgical treatment can equally well be undertaken while treatment with adrenocortical hormones is continued, with confidence that healing of intestinal anastomoses will be normal

4 of our patients underwent operations for chronic peptic ulceration (partial gastrectomy 3 cases , vagotomy and gastroenterostomy 1 case) , in all the cases the postoperative course was uneventful and recovery rapid The end-results of these operations were uniformly satisfactory, and adrenocortical hormone treatment has been continued successfully

6 other patients required emergency surgery for complications 3 for perforation and 3 for hæmatemesis Cases 1, 11, and 15 all had the classical symptoms and signs of acute perforated peptic ulcer , none was much shocked, all were operated on early, and all made rapid recoveries, though 2 later had to have more radical surgery

3 patients had massive bleeding case 8 recovered quickly and well from emergency partial gastrectomy , but cases 13 and 14 died Both the patients who died presented gross clinical evidence of hormone overdosage, whereas case 8 did not Case 13 appeared to be in good general condition despite massive and repeated hæmorrhage, and he might have been saved if he had been operated on before he became severely shocked

Case 14 died from a succession of gastrointestinal hæmorrhages caused by widespread oozing from a thin friable mucosa For many days, in spite of almost continual hæmorrhage, his general condition seemed good , any patient not receiving adrenocortical hormones who endured such a severe series of hæmorrhages would probably have appeared more ill and would have been submitted to surgery sooner than this patient was As it happened, little could be done surgically to arrest the bleeding

Although these patients presented the classical signs of perforation or of hæmorrhage, their general appearance belied the severity of the condition , this may lead to dangerous delay in undertaking appropriate surgical treatment We therefore suggest that surgery should be considered earlier for patients under treatment with corticosteroids than the usual criteria would indicate

Surgery and Bacterial Infection

The earlier views of the dangers of corticosteroid therapy in the presence of infection have been considerably revised It is now accepted practice to use the hormones in combination with antibiotics in treating certain infections There is still reluctance to operate on an infected focus while these hormones are being given, but in 5 instances where operation was done in a septic field no unusual measures were needed, and resolution was rapid and uneventful

Case 18 had suppurative otitis media which repeated courses of antibiotics did not cure Operation was delayed for several weeks because the patient was receiving prednisolone, but after radical mastoidectomy the discharge ceased and the wound healed quickly by first intention

Case 17 had chronic suppurative maxillary sinusitis which had resisted repeated lavage Bilateral nasal antrostomy led to rapid resolution although treatment with corticotrophin was continued, and the infection has not recurred ten months after operation

Case 19 had severe orbital cellulitis with suppuration Drainage of the abscess, penicillin, and anticoagulants led to complete recovery within three weeks , treatment with corticotrophin was not interrupted

Case 11 had extensive dental caries and pyorrhœa Dental clearance was done in two stages under penicillin cover, and healing was rapid and complete At this time she was receiving prednisone 20 mg daily

Pituitary-adrenocortical Suppression

Acute stress, such as a surgical operation, in some way stimulates secretion of corticotrophin by the pituitary gland, and this in turn leads to increased secretion of adrenocortical hormones But therapeutic administration of these hormones inhibits the normal mechanism , and, after such treatment has been discontinued, pituitary and adrenocortical functions remain impaired for days and occasionally many months (Salassa et al 1953b) During this period the response to stress is subnormal, and any severe stress may cause death from acute adrenocortical insufficiency Death or severe shock from this cause has been reported by Fraser et al (1952), Salassa et al (1953a), Lundy (1953), Robinson et al (1953), Harnagel and Kramer (1955), Downs and Cooper (1955), Richman et al (1956), Hayes and Kushlan (1956), Allanby (1957), and Slaney and Brooke (1957)

It is therefore imperative that the administration of adrenocortical hormones be continued throughout the operation and postoperative period If the operation is more than minor, a larger dosage of hormones must be given to allow for the increased requirement which the patient's own pituitary-adrenal system will not supply This additional dosage can conveniently be given in the form of one or two intramuscular injections of cortisone, because absorption by this route is slow, and the maximal effect may not be reached before twelve hours For the same reason intramuscular cortisone alone cannot be relied on for the treatment of acute adrenocortical insufficiency during or after operation, should this arise, hydrocortisone in addition should be administered intravenously by continuous drip

The management of patients receiving corticotrophin is more difficult The great variation in individual response and in the potency of different preparations and batches of corticotrophin makes any system of nominal dosage meaningless Treatment can be controlled satisfactorily only if the urinary excretion of 17-hydroxycorticosteroids is measured regularly, as an index of the amount of adrenal stimulation Our practice has been to continue giving corticotrophin over the period of operation and to base any alteration of dosage on the daily excretion of 17-hydroxycorticosteroids As with the patients having oral hormones, hydrocortisone can be given intravenously if signs of acute adrenocortical insufficiency develop

Conclusions

Operations during long-term treatment with adrenocortical hormones *carry no increased risk of complications*, provided that there are no gross signs of overdosage with the hormones, and the administration of the hormones is not interrupted

Summary

Thirty-six operations done during treatment with either adrenocortical hormones or corticotrophin are reviewed

Wound healing was uneventful after thirty-three of these operations

Bone repair was normal apart from non-union of a fractured neck of a femur

2 patients died and 1 recovered after gastrectomy for gastrointestinal hæmorrhage

Three elective operations for peptic ulceration and three emergency operations for perforation were uneventful

Five operations in the presence of sepsis were uneventful

Postoperative complications were insignificant

Except in 1 case hormone treatment was continued throughout the operation and postoperative period

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LABORATORY DIAGNOSIS OF CONGENITAL GALACTOSÆMIA AT BIRTH

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HITHERTO the incapacity of some infants to metabolise galactose normally has not been discovered until signs and symptoms of galactosæmia have been produced by ingestion of milk The clinical syndrome, which is probably due to disturbance of normal carbohydrate metabolism consequent on an accumulation of galactose-1-phosphate in the tissues (Schwarz, Golberg, Komrower, and Holzel 1956) could be avoided if the child's abnormality were recognised before any milk was given

We report here a method of recognising the abnormality soon after birth The test is made on cord blood, and thus involves no risk or inconvenience to the baby The reagents and equipment used are readily available in hospital laboratories

Principle

The method is based on the observation that incubation of galactosæmic erythrocytes with galactose leads to accumulation of galactose-1-phosphate in the cells The amount of galactose-1-phosphate which accumulates in normal erythrocytes in such circumstances is much smaller

The erythrocytes are incubated first with galactose and then with glucose, the free sugar is washed out with saline solution, after removal of protein the total organic and inorganic phosphates are precipitated as barium salts, and the galactose- and glucose-1-phosphates are selectively hydrolysed to free galactose and glucose These sugars are then separated chromatographically, and the amount of galactose is estimated by comparison with known quantities chromatographed simultaneously

Method

Heparinised cord blood, within 1–2 hours of collection, is introduced in a siliconed graduated 15 ml centrifuge tube up to the 2 ml mark Another sample is taken for determination of the hæmatocrit A solution of 2% galactose in saline solution (0 02 ml) is added, the tube is stoppered, and the contents are mixed The blood is incubated at 37°C for 2 hours with occasional mixing Ice-cold saline solution is then added to about 12 ml and, after mixing, the cells are spun down at medium speed, and the supernatant fluid is removed The washing is repeated twice with 12 ml of saline The cells are then reincubated with occasional mixing for 2 hours at 37°C with 0 1 ml of 2% glucose in saline and enough saline to give a volume of 2 ml The cells are washed three times with 12 ml of saline to remove free glucose

The cells are lysed by shaking with 2 vols of water containing a little saponin, and freezing Ice-cold 20% trichloracetic acid (3 vols.) is added, and the mixture is kept in ice for 6 minutes with occasional hard shaking After the mixture has been centrifuged in ice-cold buckets for 2 minutes, its total volume is recorded, and it is poured through a sintered-glass filter To the filtrate, whose volume is measured, 2 drops of 25% barium acetate is added, followed by a slight excess of 40% NaOH (phenolphthalein being used as the indicator) It is important to carry out these last operations quickly and to keep the mixture cold while the pH is acid, since the galactose-1-phosphate is readily hydrolysed in acid solution The phosphates are precipitated quantitatively by the addition of 4 vols of ethanol and by being kept in the refrigerator at least one hour (or overnight)

The precipitate is spun down, the supernatant removed, and the precipitate washed once with 5 ml of-neutralised ethanol After addition of 1 5 ml of water the precipitate is broken up with a glass rod, and the mixture is neutralised to phenolphthalein with *N* HCl and then made 0 1 *N* acid by the addition of 0 1 vol of *N* HCl The phosphates are hydrolysed by immersion of the mixture in boiling water for 7 minutes

After cooling, about 0 5 ml of water is added, followed by a slight excess of *N* H_2SO_4 to precipitate the barium The mixture is neutralised with 2*N* NH_4OH and centrifuged The supernatant fluid is transferred to a small evaporating-cup, made by cutting off a test-tube of 1 5 cm diameter about 2 cm from the bottom The precipitate is washed twice with 0 2 ml of water, and the washings are transferred to the cup The solution, which contains the free galactose and glucose derived from easily hydrolysable phosphates, together with some other components, as well as ammonium sulphate and chloride, is evaporated to dryness in a vacuum desiccator over $CaCl_2$

The dry residue is allowed to absorb some moisture from the atmosphere to facilitate grinding This is done with a small glass rod with an enlarged rounded end in the presence of 0 1 ml of pyridine, which extracts the free sugars After thorough grinding, the "slurry" is transferred with a pasteur pipette to a hæmatocrit tube The residue in the cup is ground twice, with each time 0 06 ml of pyridine, to complete the extraction and to transfer the "slurry" to the tube After the contents have been mixed by shaking up and down the tube several times, the solids are sedimented by sharp centrifugation for 4 or 5 minutes

The height of the liquid column, excluding the sediment, is noted, and half is transferred with a capillary tube to the starting-line of a descending chromatogram This is run on a sheet of no 4 Whatman paper, 58 cm long, with a 10 cm long folded strip of paper stapled to the bottom Known amounts of galactose (5, 10, 20, and 30 μg) are placed alongside the sample Without prior equilibration the chromatogram is run overnight in *n*-butanol/pyridine/water (30/20/15 by vol) (Jeanes et al 1951) After drying in a current of cold air the chromatogram is dipped in freshly prepared benzidine reagent (0 5 g of decolorised benzidine in 5 ml of glacial acetic acid, 20 ml of acetone, 4 ml of 100% trichloracetic acid, and acetone to 100 ml , added in that order) (Harris and MacWilliam 1954) The chromatogram is heated for 2–4 minutes in an oven at 100°C until the paper begins to turn pale yellow

The amount of galactose in the sample is estimated visually by comparison with the known amounts, either in daylight or in ultra-violet rays, in which the spots exhibit a bright greenish yellow fluorescence From this the amount of galactose accumulating in 1 ml cells per 2 hours is calculated

The complete test can be carried out in 2–3 days but requires relatively little attention

Results

The cord blood of 18 normal babies and the venous blood of 2 babies with galactosæmia were examined by this method, with the following result

Normal blood (mean) 3 5 μg of galactose per c cm of red cells (range 0 7–9 8)		
Galactosæmic blood	case 1	58 μg of galactose per c.cm of red cells
	case 2	76 μg of galactose per c cm of red cells

Diagnosis of Galactosæmia in a Newborn

The cord blood of case 3, sib to case 2, was examined by the method described above In addition, a sample of this blood, without incubation with galactose, was analysed for galactose-1-phosphate to find out whether any galactose had accumulated in utero The results were

Galactose-incubated blood	108 μg	(±12) of galactose	per c.cm
Unincubated blood	35 μg	”	”
Hence accumulation of galactose-1-phosphate during incubation	73 μg	”	”

On the basis of this test a diagnosis of galactosæmia was made on the third day of life, in the absence of any clinical symptoms The baby, initially fed on glucose-saline solution, was put on the milk-free diet described by Holzel (1954), she weighs 11 lb 10 oz at the age of 17 weeks and is developing normally

Discussion

We have shown previously (Komrower, Schwarz, Holzel, and Golberg 1956) that a galactose-tolerance test may not be without danger to an infant suffering from congenital galactosæmia The laboratory test described here enables a diagnosis to be made without recourse to the galactose-tolerance test and in the absence of any clinical symptoms and signs of the disease, thus eliminating the possibility of interference in the physical and mental development due to the injurious effect of galactose

Obviously, the test cannot be applied to all newborn infants, so as to detect the sporadic case of galactosæmia , but it could be applied to every newborn infant with a family history suggestive of the disease

The margin between the behaviour of normal and galactosæmic erythrocytes is wide and should enable a firm diagnosis to be made on the basis of the described test

Our experience with case 3 shows that galactose-1-phosphate may accumulate in the tissues in utero, in spite of some restriction of milk intake by the mother during gestation No galactose was detected in the mother's venous blood on two occasions after the consumption of a pint of milk At parturition no galactose was found in the liquor amnii (less than 0 04 mg per 100 ml) We do not know whether the relatively small amount of galactose-1-phosphate present in the erythrocytes at birth is matched by a similar concentration in other tissues, but it is not unlikely that the liver may contain more Nor can we say at this stage whether such small concentrations are injurious

It is hoped that the institution of a milk-free diet from birth, as made possible by the new test, will prove to be of real benefit

We have found the new test, in a slightly modified form, useful for establishing the diagnosis of untreated cases (The modification consists in omitting the incubation of the cells with glucose or galactose) Thus a four-week-old baby, presenting with the usual symptoms, was found to have 210 μg galactose per c cm of red cells in the form of galactose-1-phosphate Since this phosphate disappears only very slowly from the cells, the diagnosis can be made even in the absence of galactose from the blood and urine

Summary

A diagnosis of congenital galactosæmia can be made, within 2–3 days of birth, by a test performed on cord blood The infant can be given, from the first, a galactose-free diet and can thus be saved from the damaging effect of extraneous galactose

The test is useful for establishing the diagnosis of untreated cases

A case is described in which the diagnosis was made in this way in a newborn infant Her erythrocytes contained galactose-1-phosphate at birth, which showed that some galactose had entered the tissues in utero, though it had not been detectable in the mother's blood

We wish to thank Dr K D Coorey for his cooperation in securing the samples of normal cord blood, and Miss I M N Simpson for her able technical assistance

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TORSION OF THE STOMACH
AS A CAUSE OF VOMITING IN INFANCY

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Although an organic cause is evident in many cases of vomiting in infancy, many infants are still recorded as having neuropathic or habitual vomiting

From radiological examination of such patients we noticed for the first time, about five or six years ago, a characteristic shape and position of the stomach in some of the cases Since then we have found these characteristics with increasing frequency, and up to May 1, 1957, we had diagnosed this condition in 54 children (34 boys and 20 girls), ranging in age from one day to three years

The radiological findings are strikingly alike in all cases The body of the stomach is raised, with the greater curvature as the highest point and the lesser curvature as the lowest The posterior wall of the stomach points forward, and the pyloric antrum and pylorus with the duodenal bulb are directed more or less straight down The middle part of the transverse colon is interposed between the liver and the anterior abdominal wall and comes above and in front of the stomach, often even just under the diaphragm The following cases are illustrated in fig 1

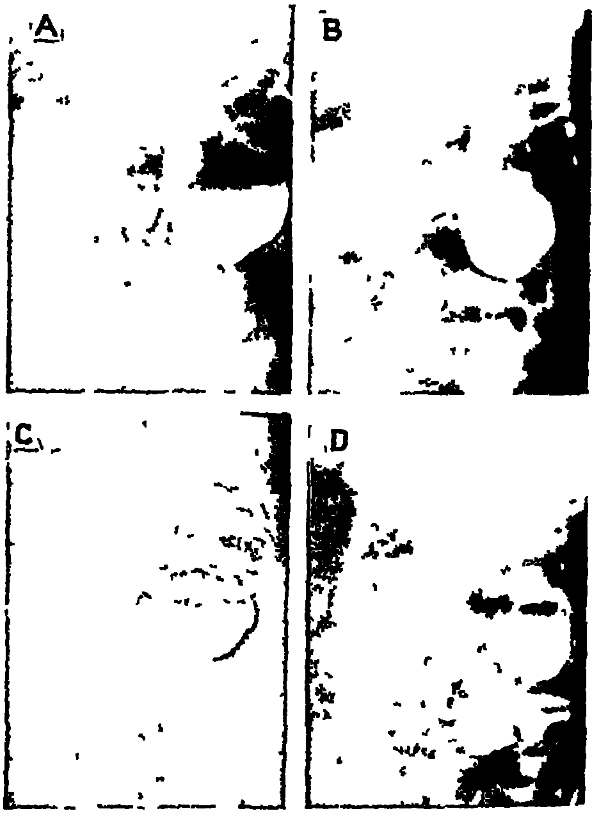

Fig 1—Findings in cases A–D See text

Case A—A girl, aged 6 weeks, with vomiting after feeds from the age of 2 weeks, never projectile Gained weight Immediate improvement when she was placed on her right side

Case B—A boy, aged $2^1/_2$ months, had from the age of 2 days uncharacteristic vomiting after practically all feeds Unsatisfactory gain of weight Vomiting ceased when he was placed on his right side

Case C—A boy, aged 4 weeks, had daily projectile vomiting from first day of life Gained weight Immediate improvement when he was placed on his right side

Case D—A girl, aged 3 weeks, had projectile vomiting from first day of life Loss of weight Immediate improvement when she was placed either prone or on her right side

Causation

Normally the stomach is fixed at two points—the cardia and the pylorus At the cardia it is fixed by the upper part of the hepatogastric ligament and by the gastrosplenic ligament At the pylorus the duodenum is fixed behind the peritoneum The rest of the stomach is suspended freely by the hepatogastric ligament The transverse colon is normally suspended below the greater curvature of the stomach by the thin and short gastrocolic ligament

In infants the lower thoracic aperture is relatively open and the liver easily mobile In the supine position the anterior edge of the liver descends,

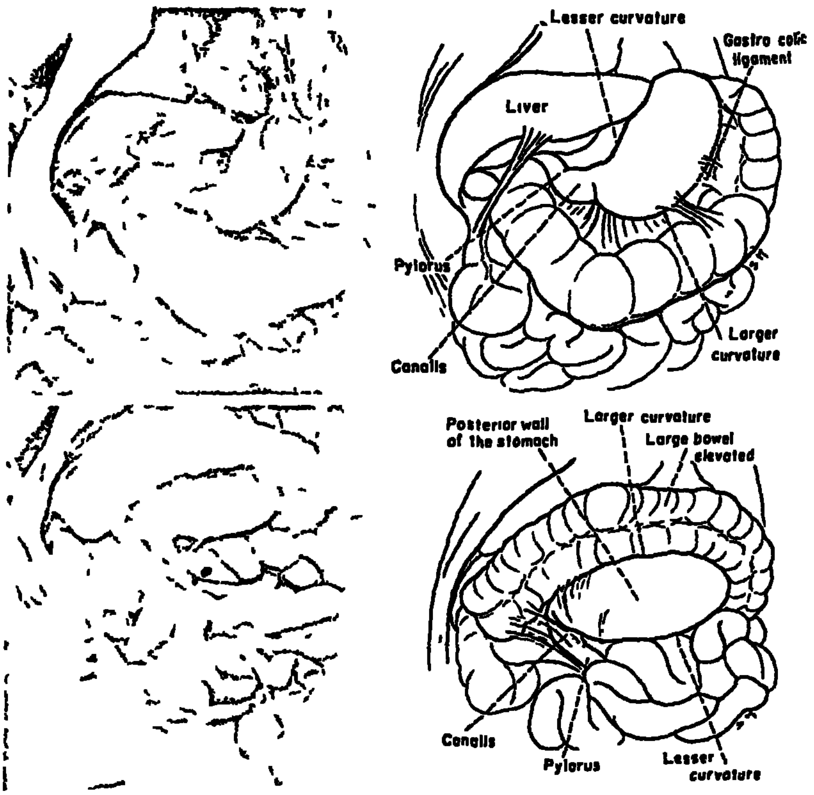

Fig 2—Artificial rotation of stomach post mortem

Above stomach and transverse colon in normal position but inflated with air Below air-filled transverse colon placed above and in front of stomach, rotating stomach through 180 and bringing posterior wall of stomach to point forwards, with greater curvature as highest point and lesser curvature as lowest point Pyloric antrum and pylorus with duodenal bulb is directed straight downwards exactly as in radiographs (fig 1)

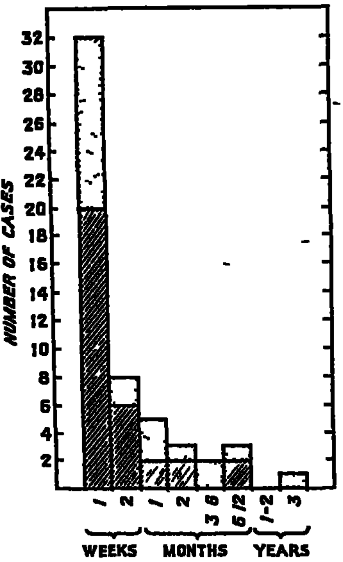

Fig 3—Age-incidence of onset of symptoms Hatched histograms, projectile vomiting

and a space may open between the liver and the anterior abdominal wall, into which a gas-filled transverse colon may easily rise In these circumstances the transverse colon pulls the stomach and twists it on its longitudinal axis with the cardia and pylorus as fixed points

This mechanism of twisting can be reproduced post mortem (fig 2) In our experience this twisting has never been more than 180° and it can be less The twisting may delay gastric emptying, interfere with peristalsis, and perhaps also disturb the circulation of the blood in the stomach

Symptoms

Vomiting beginning soon after birth is the main symptom (fig 3) Vomiting is often observed in the very first days after birth, but it may also begin later Our eldest patient was 3 years old The symptoms often start as gulps which increase to vomiting More than half the patients were observed to have projectile vomiting

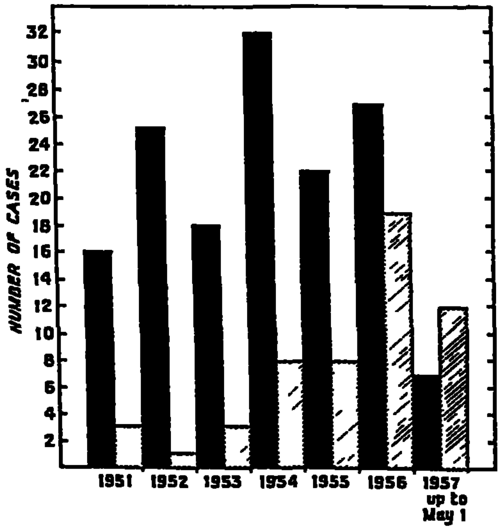

Fig 4—Incidence of twisting of stomach (hatched) and of congenital pyloric stenosis (black)

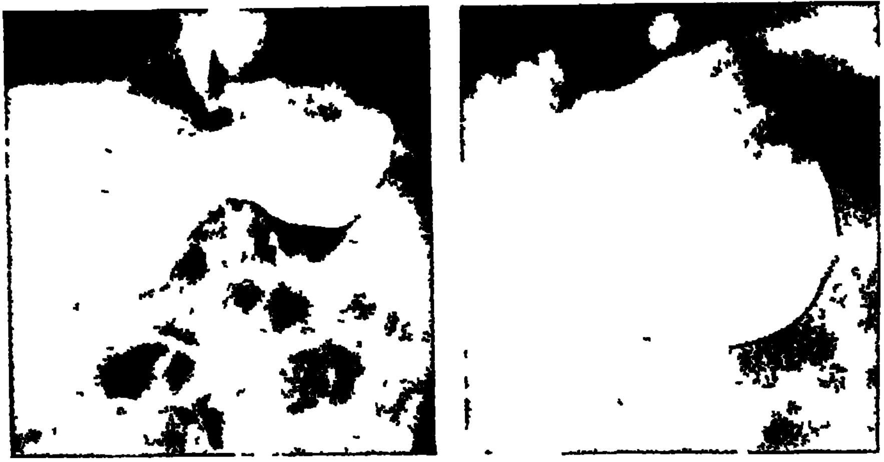

Fig 5—Stomach untwisted by holding baby head down Left before Right after

Vomiting did not always occur immediately after feeding, its force and frequency varied, but usually it occurred daily Of the 54 patients 18 gained weight satisfactorily in spite of daily vomiting, 21 gained little or no weight, and 15 lost weight

Patients with twisting of the stomach usually do not present so serious a clinical picture as infants with congenital pyloric stenosis, but it is often impossible to distinguish clinically between the two conditions In twisting of the stomach a pyloric tumour, of course, cannot be palpated Of the 54 patients 43 had vomiting as the only symptom in the remaining 11 the child was admitted to hospital for some other condition such as eczema, congenital heart-disease, epilepsy, or cerebral palsy

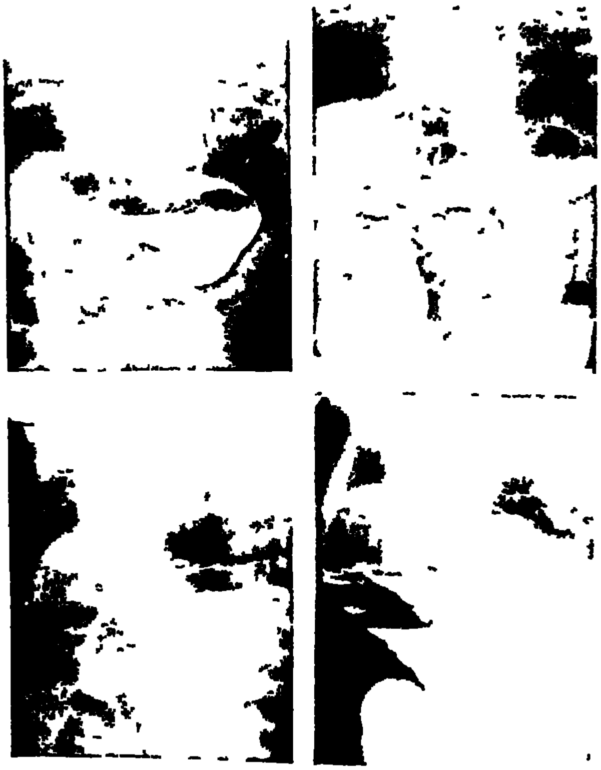

Fig 6—Unsuccessful attempt to untwist stomach by loading transverse colon with barium in a boy, aged 7 weeks Left before Right after Above left anterior oblique Below left lateral

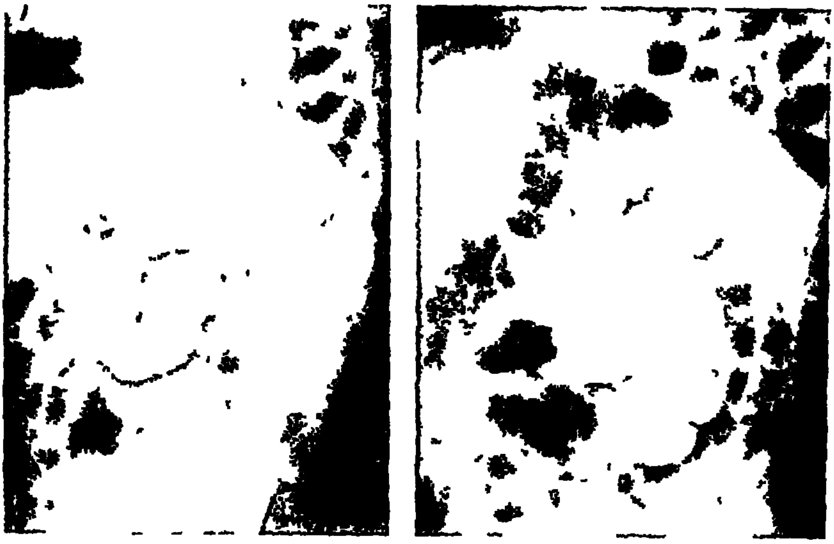

Fig 7—Twisting of stomach produced by inflation of transverse colon per rectum in a boy, aged 7 weeks, with increasing vomiting since age of 3 weeks

No projectile vomiting Unsatisfactory gain of weight. Immediate improvement when boy was placed on his right side Left stomach approximately in normal position before inflation of colon Right after inflation radiograph shows typical twisted stomach with transverse colon above it

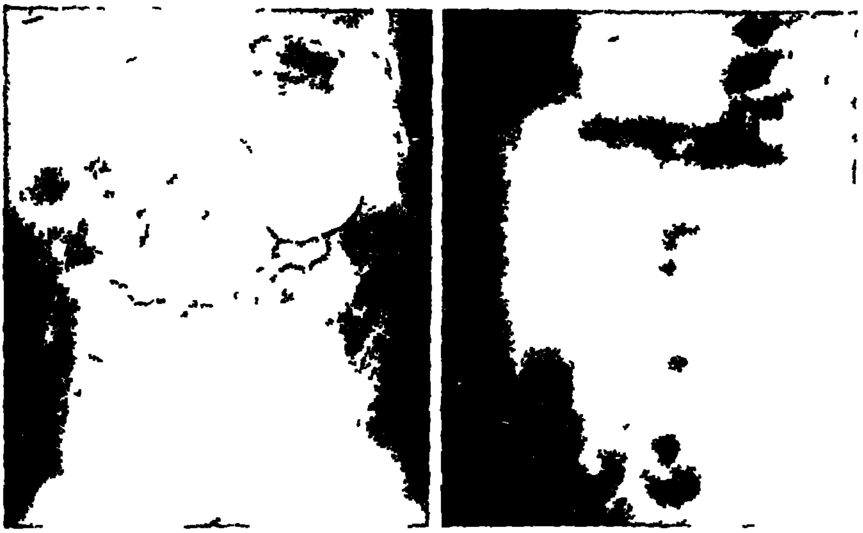

Fig 8—Intermittent twisting of stomach in a girl, aged 1 week, with vomiting from birth Left stomach normal in shape and position Right: typical twisted stomach three days later

Incidence

The condition is not rare In 1956 and the first four months of 1957 it was diagnosed in about the same number of cases as congenital pyloric stenosis (fig 4) The greater number of cases found in recent years is due to the care with which we have sought it We have not accepted clinical diagnoses such as habitual vomiting, nervous vomiting, and rumination, and every case of vomiting has been radiologically examined

X-ray Examination

Torsion is best displayed when the patient is examined in the erect position He is placed in a special cotton garment, suspended by four straps, which at the same time hold the head erect

The degree of twisting depends on the position of the transverse colon As stated, it has never exceeded 180°

We have tried to untwist the stomach by holding the patient head down to induce the transverse colon to move towards the pelvis This has only rarely been successful, as in the following case

Case E —A boy, aged 6 weeks, had vomited from the age of 2 weeks No projectile vomiting Satisfactory gain of weight. Did not vomit when placed on his right side Typical radiograph. When he was held head down, the stomach regained a normal position (fig 5)

We have also tried to untwist the stomach by filling the colon with barium, hoping that the weight of the barium might bring the transverse colon back into its normal position These attempts failed (fig 6)

In one case in which torsion was suspected the stomach appeared to be in its normal position on radiography, but we *confirmed* the diagnosis by *inflating* the transverse colon per rectum and thus twisting the stomach (fig 7) This goes to show that torsion of the stomach may sometimes be intermittent, therefore normal appearances on radiography are not conclusive, and the typical shape and position of the twisted stomach may be found at a subsequent examination (fig 8)

Treatment

The treatment is very simple The patient should be *placed* prone, with the upper part of his body lowered, or alternatively merely placed on his right side. Usually vomiting will cease immediately or become noticeably less In a few cases the vomiting may continue for some time In no case has it been necessary to untwist the stomach surgically

Comment

Since we became interested in this condition we have diligently tried to find references to it Torsion of the stomach in adults is well known (Dalgaard 1952), but the only mention of it in infants appears to be by Roviralta (1949), who called it "la plicature de la grande courbure de l'estomac" He made no mention of the cause

Summary

Torsion of the stomach is common in infants

A collection of gas raises the transverse colon to a position between the liver and the anterior abdominal wall , and the colon, being attached to the greater curvature of the stomach through the gastrocolic ligament, twists the stomach forwards and upwards

The chief symptom is vomiting, sometimes projectile, and usually beginning soon after birth

Treatment is simple the baby is placed either prone or on its right side

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A NOTE ON THE RELATION OF APPETITE TO EXERCISE

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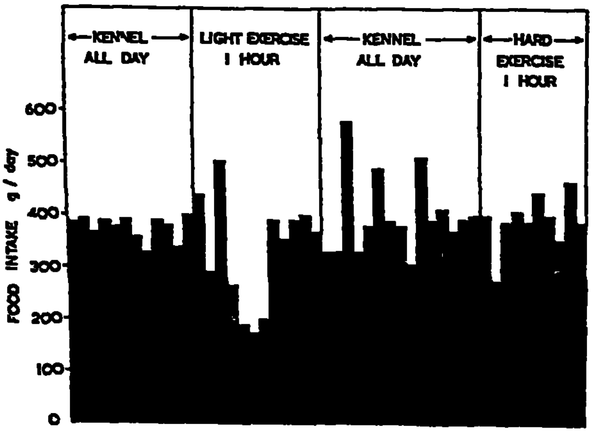
MEDICAL writers often discount the value of exercise in the treatment of obesity, because it is alleged that the extra physical activity will promote appetite, and the energy value of the extra food consumed will be the same as, or even more than, the energy value of the exercise There is, of course, no doubt that in physically active persons appetite balances, with remarkable precision, the energy values of the food eaten and the work performed But this may not be so in sedentary people

Mayer et al (1954) showed that when rats were made to walk on a treadmill for periods ranging from 1 to 6 hours daily, food intake was related to the duration of exercise and their weight was maintained constant If, however, exercise was restricted to less than an hour, there was no corresponding fall in food intake Indeed, more, not less food was eaten, and the animals gained weight I have long thought about ways and means of repeating this elegant experiment on man, but the psychological difficulties appear insuperable Recently, however, an opportunity arose to repeat their observation on a dog, which had become moderately obese during a period when it was kept in the animal-house and had free access to a liberal mixed diet

This dog was put on a diet consisting of equal parts of brown bread and a proprietary preparation of dog meat, minced together A weighed amount of food was put in the kennel each day at about noon, and removed as soon as the dog had finished eating The residue of food was then weighed This regime was continued for 49 days

During days 1–12 and 25–39 the dog remained in the kennel throughout On days 13–24 it had an hour's light exercise (walking on a treadmill on the level at 3 5 m p h), and on days 40–49 it had an hour's hard exercise (walking on a treadmill at 3 5 m p h up an incline of 1 in 10) The dog readily accomplished this and was not exhausted at the end

The figure shows that on some days when light exercise was taken the food intake was reduced, and that throughout the period of hard exercise, it was the same as in the two sedentary periods Average daily food consumption was 378 g during the first sedentary period, 331 g during the period of light exercise, 396 g during the second sedentary period, and 391 g during the period of hard exercise



There was a slight loss of weight during the sedentary periods (attributable perhaps to the limited access to food) but this loss was increased by the exercise, and over the whole period the weight fell from 25 0 to 22 6 kg The dog was very fit at the end of the studies

In this animal, clearly, a short period of exercise did not increase the appetite above the sedentary level The result is thus in line with the study of Mayer et al , and supports their suggestion that a certain minimal level of physical activity is necessary for the appetite to function with precision and to adjust food intake to requirements

If this hypothesis can be substantiated in man, it has great practical importance in the treatment of obesity It is not generally realised how sedentary is the life led by most urban people Even young military cadets spend 17³/₄ hours a day either lying, sitting, or standing (Edholm et al 1955) , the corresponding figure for coalminers is 18³/₄ hours a day and for colliery clerks 20 hours a day (Garry et al 1955) Military cadets and miners have two of the most physically active occupations, and yet about three-quarters of their life is sedentary The daily physical activity of many thousands of light workers (and housewives may be so defined—see Durnin et al 1957) may be below the threshold needed for appetite to function normally For this reason they may overeat and become obese If this is so, then perhaps the first duty of their physician is to prescribe a suitable regime of physical activities

I am indebted to the Medical Research Council for an expense grant

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Preliminary Communication

AN ANTIBODY TO CASTLE'S INTRINSIC FACTOR

WE have succeeded in producing antibodies to preparations of human and pig intrinsic factor (I F) as the initial part of a scheme to demonstrate the site of secretion of I F

Three antigens have been used One was made from human gastric mucosa (substance E of O'Brien, Taylor, Turnbull, and Witts [1]) and the other two were partially purified preparations of pig pylorus, designated I F 1345 and I F II B2 In each case the antigen was dissolved in water and emulsified with a light paraffin oil, ' Bayol F ' (Esso Standard Oil Co), containing killed human *Mycobacterium tuberculosis*, and an emulsifying agent, ' Arlacel A ' (Atlas Power Co , Wilmington, U S A) Rabbits were injected with one of the three mixtures by multiple subcutaneous puncture This Freund adjuvant technique [2] was used because it is known to give high titres of antibody, which persist for long periods

Simple precipitation tests, using all three antigens and antisera, gave heavy precipitates from interaction of the human I F and the corresponding antiserum Both pig preparations and their corresponding antisera behaved similarly There was also some cross-reaction between I F 1345 and the rabbit anti-human-I F serum Results with the Ouchterlony

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[1] O Brien J R P Taylor, W H , Turnbull A L., Witts, L J *Lancet*, 1955, i, 847

[2] Freund J McDermott K *Proc Soc exp Biol , N Y* 1942, 49 548.

INHIBITION OF INTRINSIC-FACTOR ACTIVITY BY ANTISERA

Patient no	Preparation given	Percentage absorbed of 0 5 µg dose of ^{60}Co-labelled vitamin B_{12}
1	Vitamin B_{12} alone	5 2
	" " with 20 mg I F II B2	44·4
	" " with 20 mg I F II B2 + 20 ml normal rabbit serum	47 7
	" " with 30 mg I F II B2 + 20 ml anti-pig-I F serum	
	(*a*) supernatant	21 2
	(*b*) precipitate	7 2
2	Vitamin B_{12} alone	12 6
	" " with 20 mg I F II B2 + 20 ml normal rabbit serum	55 9
	" " with 20 mg I F II B2 + 20 ml anti-I F serum	
	(*a*) supernatant	0 0
	(*b*) precipitate	9 8
3	Vitamin B_{12} alone	18·0
	" " with 10 mg I F II B2	52 1
	" " with 20 mg I F II B2 + 20 ml normal rabbit serum	63 5
	" " with 20 mg I F II B2 + 20 ml anti-pig-I F serum	
	(*a*) supernatant	5 8
	(*b*) precipitate	37 3
4	Vitamin B_{12} alone	27 3
	" " with 26 mg substance E	60 4
	" " with 26 mg substance E + 20 ml anti-human-I F rabbit serum	2 9
5	Vitamin B_{12} alone	26 6
	" " with 26 mg substance E + 20 ml normal rabbit serum	39 3
	" " with 26 mg substance E + 20 ml anti-pig-I F rabbit serum	0 0

technique,[3] in which solutions of the antigen and antiserum are allowed to diffuse towards each other from cups cut in 1% agar in petri dishes, have suggested that in the case of I F 1345 the antigen consisted of more than one constituent Substance E gave only one band with its antiserum, but this was a very weak one and cannot be taken as conclusive evidence of homogeneity

None of the antigens used was pure I F, and the only means of determining whether antibody to I F was present in the antisera was by specific neutralisation of I F activity

I F activity was estimated by the fæcal excretion method of Heinle et al [4] in patients with pernicious anæmia controlled by treatment Amounts of I F known to possess demonstrable activity were dissolved in water and mixed with antiserum in the proportions suggested by previous precipitation tests The mixture, or the precipitate and supernatant separately, was administered with the test dose of ^{60}Co-labelled vitamin B_{12} Controls were done in the same manner, using normal rabbit serum I F activity could not be tested in the case of I F 1345 by the fæcal excretion method, since it already contained a relatively large amount of vitamin B_{12}

The results are shown in the table It can be seen that human and pig I F activity can be inhibited by specific rabbit antisera

Unless some means of splitting the antigen-antibody complexes differentially can be found, serological techniques are not likely to offer a possible method of I F purification, but, using the Ouchterlony plate method, they may provide a useful means of testing the homogeneity of I F preparations and add to the established criteria of purity

It is interesting that the rabbit is able to produce an antibody to I F It may be that I F is essentially an external secretion and causes sensitisation when it is introduced parenterally, or it may be that I F is partly or wholly species-specific Schwartz et al following up their original observation that patients with pernicious anæmia may become resistant to orally administered I F,[5] have recently [6] suggested that this phenomenon may be due to such sensitisation

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New Inventions

A PLEURAL-BIOPSY PUNCH

THIS instrument enables a biopsy specimen to be taken from the parietal pleura, when an effusion is aspirated, without risk of damage to the lung It is large enough to take a satisfactory specimen (4 mm in external diameter) without causing more discomfort than ordinary aspiration under local anæsthesia Because the biopsy is clean-cut, the histological picture is undistorted

Fig 1 shows all the features of the punch except the stylet It consists essentially of two concentric tubes The short trocar point is sharp enough to penetrate the chest wall after a tiny incision has been made in the skin, but it does not puncture the lung if the effusion is completely aspirated Behind the point is a deep notch in the outer tube, which can be closed by twisting the back hexagonal grip clockwise, so sliding the pin on the base of the inner tube along the oblique slot in the base of the outer tube and advancing a sharp-cutting cylinder just past the notch with a rotary movement, thus cutting off and holding any tissue engaged therein In fig 1 the notch is seen half-closed A spring clip holds the pin in either the open or the closed position sufficiently firmly to prevent inadvertent movement

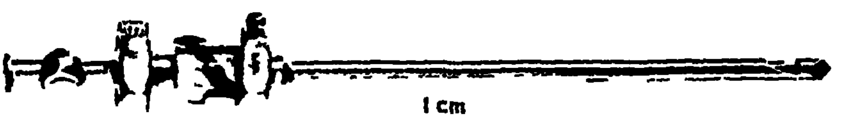

Fig 1—Pleural-biopsy punch with notch half-closed

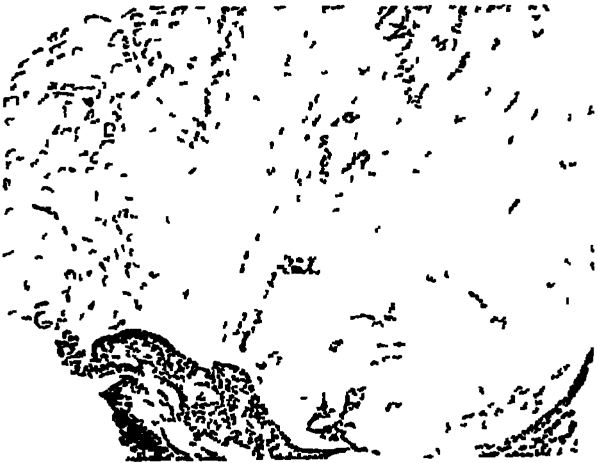

Fig 2—Pleural biopsy specimen showing intercostal muscle and thickened pleura infiltrated by carcinoma

Any type of syringe mount may be specified, so the punch can be used with apparatus for routine aspiration The two tubes can be completely separated for cleaning, and as all the parts are either stainless or heavily plated, they can be sterilised by boiling

Technique — The chest wall is infiltrated with local anæsthetic in the usual way, a tiny incision is made in the skin, and the punch is introduced with the notch closed, in which state it is airtight. The aspiration apparatus is then attached to the mount on the inner tube, the back hexagonal grip is twisted anticlockwise to open the notch, and the aspiration carried out. At the end of aspiration the notch is directed along the intercostal space by means of the indicator knob on the front hexagonal grip, the punch is slowly withdrawn, and sideways pressure in the direction of the notch is maintained until it is felt to engage in the chest wall The punch is then held firmly against the chest wall, the back hexagonal grip twisted sharply clockwise, and the punch withdrawn Finger pressure for two or three minutes stops any bleeding from the puncture The biopsy specimen is found either in the hollow point or inside the cutting cylinder

I have used the punch mostly as an aid in the diagnosis of pleural effusion of unknown origin in middle-aged patients

Fig 2 shows a biopsy specimen from a man, aged 56, who became very breathless in three weeks A very large yellow pleural effusion was aspirated several times After complete aspiration radiographs of his chest, bronchoscopy and bronchography failed to reveal the cause. Pleural biopsy was done with the next aspiration and showed thickened pleura infiltrated by carcinoma

I have also used the punch to obtain biopsy specimens from lung tumours in which there was good radiological evidence of adhesion of the lung The punch will take a biopsy specimen from any tissue into which it is inserted

Mestitz et al (1957) have related their experience with this punch, mostly in the diagnosis of tuberculous effusions In their series there were no serious complications in 116 biopsies I have had no complications in 30 biopsies

My thanks are due to Mr Holmes Sellors for his encouragement, and to all the consultant staff at Harefield Hospital, to Mr A L d'Abreu and Dr A Brian Taylor for allowing me to take biopsy specimens from their patients, and to Mr T F Dee for the photographs The Genito Urinary Manufacturing Company, 28a, Devonshire Street, London, W 1, made the instrument

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REFERENCE

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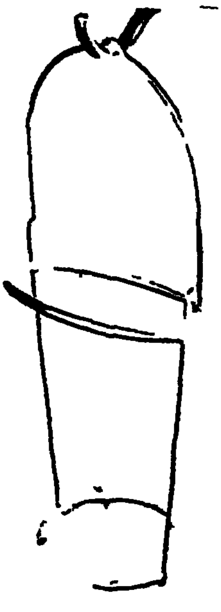
THE BRISTOL TRANSFUSION CRADLE

THIS cradle was designed to make transfusion-bottle changing an easier task, the frail wire clips supplied with transfusion sets are both awkward to fasten and unreliable when used for the second bottle



The cradle (see figure) contains two rings supported by cross-pieces with a loop for attachment to the transfusion stand The upper elliptical ring is set at an angle so that, after the upper part of the bottle has been passed through it, the bottle can rotate about a horizontal axis, its neck passing through a gap of $1^5/_8$ in in the lower ring

Cradles of this type have been in constant use for the past eight months and were found to save much labour

We are indebted to Mr A E Christmas, instrument maker at the Bristol Royal Infirmary, for assisting in the design, and Mr R. Bennett for making the trial prototypes The cradle can be obtained from Messrs Charles F Thackray Ltd, Park St, Leeds, 1

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Reviews of Books

Essentials of Chemical Pathology

D N BARON, M.D, reader in chemical pathology, Royal Free Hospital School of Medicine, London London English Universities Press 1957 Pp 247 25s

IN twenty years the subject of chemical pathology has advanced from a sideline of clinical pathology to a major specialty in its own right, influencing the development of almost every field of medicine. These broad advances have been paralleled by a literature which at present consists mainly of advanced treatises or students' elementary textbooks Dr Baron has intended his book to provide medical students, housemen, and registrars with an adequate knowledge of chemical pathology to permit them to keep up to date with this ever-advancing subject.

The first part gives a general account of the normal and abnormal features of fluid and electrolyte distribution and of carbohydrate, fat, and protein metabolism There follow details of the applications of chemistry to the investigation of various systems The section on calcium, phosphorus, and bone, and those on water and electrolytes and on acidosis and alkalosis, are exceptionally good, but the kidneys could with advantage have been discussed more fully The chapter on the steroids is particularly useful, but a clearer account might have been given of the causes of difficulty in assessment of adrenal function. There is a remarkably complete account of differential estimations of serum-proteins, and such up-to-date topics as C-reactive protein, afibrinogenæmia, agammaglobulinæmia and fibrocystic disease are included

In an introduction, Sir Charles Dodds remarks that the author has refrained from quoting a large number of references, but the book covers so wide a field that many readers would welcome further reference to certain subjects

This is in no sense a laboratory manual, though some clinical procedures, as well as various methods for routine testing of urine, are described in detail It is perhaps a pity that Dr Baron's desire for completeness has led him to describe such out-of-date tests as Hay's test, the urea-concentration test, and the hippuric-acid tests, all of which are of little clinical value It is high time, too, that osazone and fermentation tests for the identification of glucose were abolished from chemical pathological practice, identification by paper chromatography or enzyme tests is more satisfactory

The statements that "The bilirubin which is originally produced from hæmoglobin is also called indirect, pre-hepatic or hæmobilirubin The modified bilirubin which has passed through the liver is called direct, post-hepatic, or chole-bilirubin" do not emphasise the need to drop this terminology The recent classification of the mechanism of the van den Bergh reaction by Lathe has led to the more logical use of the terms "bilirubin" and "conjugated bilirubin"

The book is perhaps too detailed for general use by the student, but it deserves to be widely read by the many doctors who nowadays seek the help of the laboratory of chemical pathology At 25s it is one of the best bargains among medical textbooks

Sigmund Freud Life and Work

Vol 3 The Last Phase, 1919-1939 ERNEST JONES, M.D, F R.C P London Hogarth Press 1957 Pp 536 35s

Dr Ernest Jones may rest content with his biographical labours Confronted with the peculiar difficulties that beset a psychoanalyst in this task, he has for the most part put aside the temptation to infer and to interpret. He has given us instead a well-documented and faithful story of the struggles and vicissitudes of Freud's life, it is a good historical account, which might have been written by someone quite incapable of making a subtle psychoanalytical dissection of what lay beneath the surface, in the way that Freud himself did in his essays on Goethe, Dostoevsky, and Leonardo

Half of the third and concluding volume is devoted to the last twenty years of Freud's life—a period of great physical suffering endured with noble stoicism, and of disappointments and upheavals which he met with unfailing humour and fortitude His character matched his intellectual power, and few who have read this biography will withhold admiration and respect, however little they may agree with the tenets of psychoanalysis In the account of this last phase, Freud's daughter Anna shines with a milder light in the background, a devoted and selfless helper The volume is appropriately dedicated to her

It is a pity that Dr Jones has given so much space to personal quarrels, such as that between himself and Rank It is clear that feuds among his followers distressed Freud and sometimes took up much of his time and thought, but the detailed account of suspicions and misunderstandings makes tedious reading

The latter half of the book consists of a review of Freud's contribution to a wide range of subjects, including religion, occultism, art, and literature This is naturally a subjective valuation, crediting Freud's work with a greater and more lasting impact than many who are expert in the respective subjects have been willing to concede It affords, however, a striking conspectus of the long creative activity of a fertile and very original mind

Chemotherapy and the Central Nervous System

HENRY MCILWAIN, PH D, D SC, professor of biochemistry, University of London, at the Institute of Psychiatry London J & A Churchill 1957 Pp 328 45s

SINCE the time of Ehrlich the term "chemotherapy" has usually been restricted to chemical treatment which destroys some infecting organism (bacterium or parasite), but by its derivation it ought to include all treatment by chemical compounds Dr McIlwain uses the term in the wider sense, and his book considers chemical compounds which have been used to produce all kinds of therapeutic effects in the central nervous system

His approach is mainly historical, starting from 1800 and leading up to the most recent developments Thus, successive chapters describe general anæsthetics and hypnotics, antipyretics, the distribution of drugs in the body and their metabolism, the action of drugs on the body and on the disturbing agent, drugs acting on infections (arsenicals and other compounds against trypanosomes and syphilis, sulphonamides, and antibiotics), and the theory of antimetabolites developed from them, anticonvulsant and drugs for the treatment of epilepsy, and drugs for nervous and mental disorders, both those which are mainly excitant (e g, amphetamine, pipradol) and those which are mainly depressant (e g, reserpine, chlorpromazine) Finally, there is a chapter which considers the general principles of discovering new drugs for action upon the central nervous system

The book does not attempt to give technical details or exact data, but rather considers general principles, and the author is to be congratulated on having told a complex story in a simple and intelligible style, which does not need a detailed knowledge of chemistry or pharmacology for its appreciation He will find ready readers among doctors who are interested in knowing the background of the drugs they use, and among research-workers, pharmacologists, and synthetic chemists engaged in the search for new remedies

Gynecologic Surgery and Urology

THOMAS L BALL, M.D, assistant professor of clinical obstetrics and gynecology, Cornell University Medical College London Henry Kimpton 1957 Pp 547 150s

BRITISH gynæcologists perhaps do not realise that in many centres in the United States gynæcology and female urology are almost one specialty Dr Thomas Ball's beautiful volume of operative gynæcology might well have been entitled Female Pelvic Surgery, since it includes some basic proctology in addition to urology and gynæcology The reader will b impressed with the accurate anatomy and the thoughtf and meticulous approach of the anatomically trained surgeo to each clinical problem, which is illustrated by some of th finest drawings to be found in any similar book

The scope is considerable and includes many importa problems which are not strictly surgical, such as the psychosomatic aspects of gynæcological surgery, and a particularl thoughtful chapter on backache in women The general substance of the book is in line with the best modern British gynæcological practice, and the style of the author is clear and at times, refreshingly racy The chapter on malignant tumours, radiation, and radical surgery is perhaps the best, and includes some of the more recent advances in radiation therapy

British gynæcologists should not be deterred by the price o this lavishly produced and generously illustrated book, for by spending it they will broaden their attitude to gynæcology and they will find much to stimulate and instruct them

The Sea My Surgery

JOSEPH MAGUIRE, M B London William Heinemann 1957 Pp 234 16s

Dr Maguire has been a ship's doctor for thirty years, and for fifteen of them he has been serving in the *Queen Mary* or the *Queen Elizabeth* Even the least gifted of writers would find it hard to write a dull book with that sort of experience behind him—and Dr Maguire is certainly not in that category He tells his story with all the gift for raconterie which on might expect from an old sailor who is also an Irishman

To remind us that, even on one of the Queens, a shi doctor's life is not concerned exclusively with tending f stars with headaches, there are several accounts of more d perate emergencies—sometimes fought out with hundreds miles separating the doctor and his patient, whose condit had to be diagnosed and treated by radio One of the m interesting chapters recalls a period when conditions were so luxurious Dr Maguire sailed in the *Queen Elizab* throughout the late war, when she was used for trooping S then carried up to 15,000 soldiers at a time, but in a mann which denied them most of the comforts the peacetime p senger expects (The better state-rooms on the main de for instance, which normally accommodated 2 persons, w reserved for colonels—26 to a room!) There are intrigu glimpses of the organisation which made possible this m transport of men, and which surmounted such tasks as cook 31,000 eggs for breakfast

The Disease of Tobacco Smoking and its Cure

LENNOX JOHNSTON, M B London Christopher Johnson 19 Pp 104 3s 6d

SMOKING has been shown to be partly responsible f bronchial carcinoma, pulmonary tuberculosis, corona occlusion, thromboangiitis obliterans, and tobacco amblyopia not to mention the fires and mine explosions it causes, and t road accidents attributable to cerebral ischæmia due to ca boxyhæmoglobinæmia There is little to be said in favour smoking, and the world would no doubt be a happier place it were abandoned Dr Johnston has been saying this wi some force for years, and he has now written a summary of t evidence against smoking, an account of his alarming expe ments on himself with nicotine, and a history of his campaig We wish him success, but we must unhappily forecast that t tone of his book will incense most smokers rather than convinc them of their errors They may be frightened into givin up their addiction, they will not be persuaded by thes methods

The book may better serve a purpose in helping those wh have decided to stop smoking, there are hints and encouragement, and suggestions for forming a stalwart mental attitud against smoking An appendix gives verbatim the recent statement by the Medical Research Council on tobacco-smokin and cancer of the lung

THE LANCET

LONDON 4 JANUARY 1958

Incidental Dangers of X-ray Therapy

Belief in the relative "radioresistance" of certain organs and tissues which may have to be included in therapeutic X-ray fields prevailed for many years But in the past decade that comfortable conviction has been rudely shaken, and to long-established hazards, such as radiation burns and bone-marrow aplasia, further disquieting possibilities have been added Major damage to the kidney, to the central nervous system, to the lung, and probably to the heart-muscle must now be included among the risks of radiation

The clinical and experimental work of Prof Clifford Wilson and his colleagues, whose report we publish this week, demonstrates that irradiation of the kidney may produce hypertension which, both clinically and histologically, is indistinguishable from malignant essential hypertension This discovery that renal hypertension can be induced without obstructing the renal circulation and in the absence of manifest renal damage is of great interest It opens new possibilities for the role of the kidney in the genesis of chronic hypertension, and particularly of essential hypertension, where a renal mechanism has hitherto appeared less likely because, in the early stages, there are no structural changes in the kidney These observations confirm and explain in a remarkable way the different clinical syndromes described by Luxton [1] in his account of radiation nephritis The pathological features of this nephritis were reported by Russell,[2] and the limits of renal tolerance to X rays were carefully assessed by Kunkler et al [3]

Boden [4] examined 161 patients who had been given X-ray therapy for malignant growths of the mouth and neck, and found 10 with radiation myelitis of the cervical spinal cord, which was fatal in 5 cases Boden [5] later reviewed 7 cases of radiation myelitis of the brain-stem, and thus confirmed and greatly expanded the work on isolated cases of Ahlbom [6] Smithers et al,[7] and Stevenson and Eckhardt [8] Cerebral damage from radiation has been similarly recognised clinically by Wachowski and Chenault [9] and Pennybacker and Russell [10] Radiation damage to the lung was first described by Groover et al [11] and was brought clearly again to our notice by Whitfield et al [12] who recorded 29 cases. Whitfield and Kunkler [13] described 4 patients with electrocardiographic changes following X-ray treatment to the thorax Furthermore, the threat of leukæmia from X-radiation seems real enough, evidence coming from studies of patients with ankylosing spondylitis treated with X rays,[14] from the incidence of leukæmia in children given X-ray treatment in infancy for enlargement of the thymus,[15] from the increased death-rate among physicians practising radiology,[16–18] and from the death-rate from leukæmia attributable to the atomic explosions in Nagasaki and Hiroshima [19–21]

Radiotherapy is of immense value as radical treatment for certain malignant growths, especially cancers of the skin, lip, tongue, and uterine cervix, and is used as palliative treatment for many other types of neoplastic disease There is also a sound basis for prophylactic irradiation of the abdomen after unilateral orchidectomy for seminoma [22]—a practice which drew attention to the nephritis caused by X rays

X-ray therapy having been in vigorous use for over thirty years, it may be asked why its clinical side-effects have not been investigated more closely Forssell [23] stated emphatically "A medical man who devotes his services to a radiotherapeutic clinic must forsake all else and be willing to devote life and soul to radiotherapy" Is the old adage relevant here—"Love is blind but the neighbours ain't"? The radiotherapist may seem somewhat uncritical of the side-effects which alarm his colleagues There are, however, important contributory factors Commonly a latent period of weeks or months divides the start of X-ray therapy from the development of symptoms of incidental X-ray damage It has been only too easy to dissociate such symptoms from the X-ray therapy and to attribute them to metastases or to an extension of the primary growth—and even to prescribe further X-radiation on that account Furthermore, a feature of X-ray therapy is the variation in susceptibility between patients, as between individual tumours Also, radiotherapy is a developing science, new techniques with incompletely known effects are constantly under trial But perhaps the main difficulty is that the radiotherapist's attention is focused on the malignant growth He knows that the patient's survival depends on its eradication, and, half-measures being fraught with peril, makes the primary treatment as radical as possible

It profits all concerned, especially the patient, if radiotherapists work in close association with clinicians "Combined clinics" are now widely established in which radiotherapist and surgeon or gynæcologist see the patients together, and seek to agree on diagnosis and treatment Radiotherapy should not be isolated It should be part of a general scheme, and those who conduct it should maintain constant contact with both physicians and surgeons in diagnosis, treatment, and

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follow-up Much is already being done to avoid the incidental dangers of X-radiation—for instance, by using megavoltage and by "shielding" techniques But radiotherapy remains a powerful weapon which can be fatal to both friend and foe, and the whole resources of medicine are required to ensure that its edge is turned always against the invader

Influenza Vaccines

THE circumstances of the recent influenza epidemic have been unique in many ways From the time when the so-called Asian viruses first appeared and showed their ability to spread, it was clear that a world-wide epidemic could be expected Accordingly in many countries, including the U S A and this country, there was a short period during which vaccine could be prepared in readiness for the epidemic Plans were made in the U S A, and to a lesser degree in this country, to use vaccine on a larger scale than ever before To some extent these plans were disorganised by the fact that the epidemic got under way well ahead of winter—the usual season for influenza epidemics At the moment the epidemic is on the wane, but a second wave may come later in the winter

It is too early yet to judge how effective the influenza vaccine has been, this information can only come from controlled trials carried out under various conditions In a small trial [1] 70 volunteers in an American State penitentiary were vaccinated last July with either Asian vaccine or an inert fluid, in such a way that neither the volunteers nor the clinical observers knew which inoculation had been given to each individual Three to four weeks later 55 of the volunteers were inoculated with live Asian virus in the form of a pool of nasopharyngeal washings collected from Boy Scouts who took ill while attending a jamboree Volunteers first received an instillation of saline into their nostrils in order to clear away all mucus, and then the inoculum was sprayed into each nostril and into the oral pharynx by means of a De Vilbiss atomiser, and the oral pharynx was also swabbed vigorously with a swab dipped in the inoculum It was calculated that each volunteer received about ten thousand infective doses of virus, corresponding to one or two drops of nasopharyngeal secretion Altogether 78% of 23 volunteers in the control group developed influenza, compared with 44% of 32 volunteers in the vaccinated group Clearly the results of this limited trial, in which an artificial method was used for inducing infection, can be taken as only a very rough guide to what may be expected under natural conditions of exposure to infection Nevertheless the findings suggest that the vaccine is unlikely to have dramatic protective effects, and unofficial reports of its behaviour under natural conditions are in line with this conclusion

The results of previous trials of influenza virus vaccine have varied, in some epidemics protection-rates of 70–80% have been found, while in others vaccine has shown no beneficial action The most variable factor is the virus itself, which seems to have an almost unlimited capacity to mutate from one epidemic to the next, and the best protection-rates have been found when the virus used in preparing vaccine was antigenically closely related to the epidemic virus The virus responsible for this latest epidemic is antigenically remote from previous influenza-A viruses [2] It is therefore possible that a single inoculation of vaccine would not protect as well as two inoculations, and this is one of the questions which may be answered by trials now in progress This possibility was suggested by a vaccine study [3] among schoolchildren in this country Unfortunately it seems that knowledge gained from one vaccine trial cannot be readily used to predict the protective value of a new vaccine in a changed epidemiological situation, and clearly we do not know enough about the epidemiology of influenza and the best use of influenza vaccines to allow us to keep one step ahead of the virus At the moment, while influenza is relatively mild and the degree of protection given by Asian-virus vaccine is still unknown, the decision how widely to use vaccine will be dictated mainly by political and economic factors

Hospital and Home

IF hopes are seldom realised in full, neither are fears At the beginning of a year which will see the tenth birthday of the National Health Service, we can take comfort from its continuing state of flux Instead of settling in a solid mould, as was predicted, it remains malleable enough to be adapted to new circumstances and new ideas of what the public needs Already some remarkable changes are beginning

Medicine, of course, is in a highly dynamic phase, which refuses to be bound by calculation and prophecy Thinking of projects into which we have put our heart, some of us may reflect half ruefully on the effort we put for instance, into pressing Governments to take tuberculosis more seriously and provide a great many more beds for its treatment On which Dr BERESFORD's letter in our correspondence columns this week is sufficient comment, for he is suggesting that the larger sanatoria should now be made over to other purposes Again, in face of the shocking overcrowding of mental hospitals, it must have seemed to many that the urgent need was to relieve pressure by putting up new buildings But the paper by Dr CARSE and his colleagues (p 39) shows once more that such thinking is out of date From the varied experience of such enterprising places as Amsterdam, Nottingham, Manchester, Bristol, Bromley, the Maudsley, and now Worthing, a quite different system of looking after mental disorder is beginning to emerge—a system in which most of the patients will go on living at home while under treatment and will get the benefits of psychiatry, at day hospital or clinic, without risk of the desocialisation too often suffered in the past by those who have entered large and often isolated institutions Within ten years, at latest, we may be wondering what to do with the many mental hospitals which are plainly unsuitable for the proper practice of psychiatry within the same framework as the rest of medicine.

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[1] Bell, J A, Ward, T G, Kapikian, A Z, Shelokov, A, Reichelderfer, T E, Huebner, R J *J Amer med Ass* 1957, 163, 1366

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[3] Hawkins, G I C, Hutch, L A, McDonald, J C *Brit med J* 195 ii, 1200

Both in tuberculosis and in mental disorder we see examples of the new tendency to treat the patient at home in his natural surroundings. Similarly it is clear that a great many old people who have been forced into institutions ought to have had the kind of help that would enable them to go on living independent lives, often far more happily. There is always a risk that, with any new movement like the present endeavour to keep patients out of hospital, one may end up by sacrificing people to the idea: there are some mental patients, and some old people, and indeed some children, who can be kept at home only at immense cost in strain to their relatives—no matter what aid they may get from doctor, home nurse, health visitor, or home help. Indeed, home care can be financially much more expensive than hospital care, and cannot therefore always be preferred even on economic grounds. Nevertheless we are certainly witnessing the development of fresh arrangements by which many more patients will visit the hospital instead of living in it. And we are also witnessing a change in the nature of the hospital itself. At last people are getting away from the rigid concept of a hospital as consisting of a collection of similar wards, each staffed by a complete hierarchy of trained nurses, to which every patient who needs specialised investigation or treatment must be admitted. Many years' experience has shown how much can be done in outpatient departments without entering the wards, and still more could be done if suitable patients could have hostel accommodation overnight. Similarly many patients necessarily admitted to ordinary wards could, as they recover, graduate to wards without nursing supervision, where some of them could virtually look after themselves while obtaining whatever treatment they need. What has been wittily called "cafeteria medicine" surely has a real future, for it is futile to waste the service of skilled nurses on people who do not in the least require them.

In returning thus to the old theme of keeping patients out of hospital, we return also to the question of where the centre of gravity of medicine really is or should be. Are the hospitals merely an appendage to general practice, where 90% of the patients are seen and treated? Or is the hospital the true temple, and the family doctors no more than mobile acolytes? We have repeatedly stated our opinion that, wherever the exact balance lies, grave damage will be done if the general practitioner ceases to regard himself as an all-round doctor capable of accurate diagnosis and treatment, and responsible for the care of patients rather than for the disposal of applicants. And in some ways the new trend towards keeping the patient at home, and bringing the specialist to his hearth, may help to restore the practitioner's position. On the other hand many of the present promising experiments—for example, the Worthing trial of domiciliary psychiatry, the Cambridge scheme for discharging patients early, with extra nursing care, the St Mary's Hospital pædiatric team which goes to illness in the home[1]—are essentially extensions of hospital work: the hospital is sending out pseudopodia, and though these may make useful contacts with general practitioners they do not necessarily increase the activity or scope of general practice. Likewise the development of hospital departments for looking after special groups of people in an area, such as the epileptic or the spastic, may lessen rather than stimulate the family doctor's sense of being in ultimate charge.

Those who care about the future of general practice should, we think, be paying close attention to the process by which the hospital is projecting itself ever further towards the home. We for our part welcome this development as often realistic and helpful, but we still believe that everyday medical care should be given by an independent family doctor, directly responsible to his patient, and not by a hospital medical officer however mobile. All too clearly, general practice on a high level is not going to be preserved unless those who have faith in it are prepared to translate that faith into works.

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[1] See *Lancet*, 1957, i, 313.

Annotations

SYRINGES: CLEAN OR STERILE?

Of the many unsatisfactory ways of attempting to sterilise syringes in hospital, the commonest is boiling. Even in favourable circumstances this method does not eliminate spores, and circumstances may be so unfavourable that non-sporing organisms escape. Thus a doctor or nurse in a hurry may use a syringe after less than five minutes' boiling, or contaminated material may be put in the steriliser just before the syringe is removed. Some hospitals now have a central service, where syringes are autoclaved and wrapped for distribution to wards and departments; others (we hope all) will want to institute one. The Nuffield Provincial Hospitals Trust has done well to produce a little book[1] which sets out clearly and concisely all the information needed for the purpose. It represents the work of an operational research team who have investigated some existing syringe services.

The first chapter is so detailed that it amounts almost to a blueprint for building a department. The second describes the most economical way of running the department, and suggests means of greater economy when newer apparatus is to be had. The third shows that the capital outlay for a capacity of 500 syringes a day would at present be about £1600 and the running costs (including syringe and needle replacements) £3725 a year, or about *5d* a syringe. A service on a national or regional scale would not be more economical than one on a group or hospital scale. Capital depreciation is not considered, and the cost of "sterilising" syringes by boiling is only briefly discussed. A central service would make for some saving in that ward sterilisers are apt to be left boiling too long, with waste of fuel, and are costly to maintain; the saving would be appreciable if all sterilisation (not merely of syringes) were done centrally.

The safety, convenience, and possible economy of central syringe-sterilising services strongly commend the method to all hospitals, and anybody planning one now has useful guidance at hand.

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[1] The Planning and Organisation of Central Syringe Services. Nuffield Provincial Hospitals Trust, Nuffield Lodge, Regent's Park, London, N.W.1. 1957. Pp 59. 2s 6d.

BARBITURATES AND GLUCOSE

It has been recognised for some years that the injection of hypertonic glucose into an animal awakening from barbiturate narcosis will reinduce anæsthesia[1] This response has been investigated in man by Dhuner and Nordquist,[2] who were prompted by the chance observation that administration of cortisone to a patient recovering from an overdose of phenobarbitone returned him to a state of deep unconsciousness (Their report appears in the first issue of *Acta Anæsthesiologica Scandinavica*[3])

A series of 20 further patients was observed, of whom 18 had had an overdose of a single identifiable barbiturate and 2 an overdose of promethazine Of these 20, 13 received 50–100 mg of cortisone intravenously or intramuscularly and 7 9–12 g of glucose intravenously in a 30% solution immediately they had awakened from the intoxication Unconsciousness, assessed clinically in all cases and by electroencephalographic tracings in 6, was reinduced in some degree in 16 cases—in 8 to a level approximating to that on admission A control series of non-intoxicated patients who received similar quantities of cortisone or glucose showed no effects of any kind

Dhunér and Nordquist cannot explain these findings They found no change in the plasma-barbiturate level after injection of glucose, but an occasional fall (which was not correlated with the clinical effects) shortly after administration of cortisone They rightly stress the potential clinical importance of such reinduction of unconsciousness not only in the treatment of barbiturate or promethazine poisoning, but also in anæsthetic practice

GERIATRICS IN THE HOME

With the Ministry of Health again rightly pointing out that old people who are unwell should if possible be cared for at home instead of being admitted to overcrowded hospitals,[4] the report of a pilot experiment in geriatric reablement in the home should be of great interest not only to administrators but to every family doctor

This experiment[5] was undertaken by the geriatric unit of the Belfast City Hospital, with the help of £5000 provided from the Nuffield Provincial Hospitals Trust, and its basis was a belief that there are elderly invalids who are getting good home care but nevertheless risk delayed recovery, or even permanent bedfastness, through lack of reablement facilities which are usually to be had only in hospital If these facilities were brought to the home, might not the burden of ill-health—on patient and relatives alike—be lightened and the demand on long-stay hospital beds lessened? The report recounts how the need was established and how the cases for trial were selected Of 272 patients initially referred by their doctors, 85 were thought suitable, 37 of these being hemiplegics and 28 cases of arthritis Medical assessment by the visiting geriatric physician was the basis of the advice on nursing management and general care In treatment the mainstay was physiotherapy—with emphasis on what the patient and relatives could do for themselves After courses of up to 50 treatments (though often much fewer) it was judged that about two-thirds made a satisfactory recovery Though the cost of the treatment averaged 15*s* 9*d* for each visit by the physiotherapist, to get similar results with the patient in hospital would have cost considerably more

Dr Adams and his colleagues are certainly not pleading for unrestricted home physiotherapy Less than a third of the patients referred were in fact thought suitable, and in making this decision good home circumstances were considered as important as a medical condition capable of improvement The conclusion that "home treatment and rehabilitation has been successful within the limits defined" is qualified by its description as "a useful aid to comprehensive home care services for the aged" rather than an end in itself For most of the aged sick at home, who would be unlikely to benefit from treatment of this kind, the Belfast team believe that more could be done if the existing services provided by statutory and voluntary bodies were better coordinated They suggest that every area should have a counselling centre to which the general practitioner could turn, and which could provide a skilled social worker (preferably a health visitor) to assess the home situation, with power to focus all the necessary services where they are needed This valuable recommendation supplements the growing feeling that such, indeed, is an important function of the health visitor of today and tomorrow

PORTOPULMONARY ANASTOMOSES IN HEPATIC CIRRHOSIS

Over twenty years ago Snell[1] observed that in some patients with hepatic cirrhosis the oxygen saturation of the arterial blood was reduced That this was not due to any impairment of gaseous diffusion from the pulmonary alveoli to the capillaries was shown by Abelmann and his colleagues[2] in Boston These findings could only mean that a considerable volume of venous blood was diluting the arterial blood in the pulmonary veins, and, since there was no reason to suppose that this was coming from underventilated areas of lung, the most probable source was portal blood shunted into the pulmonary venous system Calabresi and Abelmann[2] therefore sought to demonstrate the anastomotic channels

Anastomoses between the pulmonary and azygos veins via the bronchial veins have long been known to exist, and the possibility that portal blood followed this route was investigated In 20 cadavers the portal vein was injected in situ with a radio-opaque lead gelatin mass too viscous to enter vessels below 40 µ in diameter The mass was coloured with methyl-green so that its distribution could be readily followed both by dissection and by radiography Of the 20 bodies studied, death had been due in 10 cases to cirrhosis of the liver with ascites and in 6 to congestive cardiac failure In the remaining 4 cases there was no significant cardiac or hepatic disease In each of the cirrhotic cases there were dilated and tortuous periœsophageal veins injected via the coronary and short veins of the stomach These periœsophageal veins anastomosed freely with veins in the posterior mediastinum, with pleuropericardial veins, and, via the azygos veins, with the superior vena cava Moreover, in 4 of the 6 cadavers in which a satisfactory injection was achieved, the posterior mediastinal veins anastomosed freely with peribronchial veins at the tracheal bifurcation and with the bronchial veins of the main-stem bronchi

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1 Lamson P D Greig M E, Robbins B H *Science* 1949, 110, 690

2 Dhunér, K G Nordquist P *Acta anæsth scand* 1957, 1, 55

3 Published from Universitetsforlaget i Aarhus Aaboulevarden 49 Aarhus, Denmark 40 Dan Kr per annum Edited by Dr Eric Nilsson Department of Anæsthesiology University Hospital, Lund Sweden

4 Ministry of Health circular H M (57)96

5 Adams G F McQuitty F M Flint M Y Rehabilitation of the Elderly Invalid at Home an experiment in restoration of activity after illness amongst old people in their homes in Belfast Nuffield Provincial Hospitals Trust 3s

1 Snell A M *Ann intern Med* 1935, 9 690

2 Calabresi P Abelmann W H *J clin Invest* 1957, 36 1257

In one preparation a vessel was found running directly from the posterior mediastinal plexus to a tributary of a right pulmonary vein, while in 2 of this group the injection had reached the pulmonary veins and the left auricle and ventricle. In the cases of congestive heart-failure all 5 cadavers adequately injected showed gross anastomoses between the portal system and bronchial veins via the periœsophageal, mediastinal, and pleuropericardial plexuses, but in no case did the injection mass reach the heart or main pulmonary veins. A somewhat similar result was obtained in the cases with no cardiac or hepatic disease, but the injected vessels were invariably fewer and smaller than in the cirrhotic and cardiac groups.

The pressures in the portal and pulmonary venous systems in health are approximately the same. It is therefore theoretically possible for blood to flow from one to the other whenever the pressure in either system is pathologically raised, and the anatomical findings of Calabresi and Abelmann strongly suggest that such a diversion of flow actually occurs. Their radiographic demonstration of a dilated azygos vein in 5 living cirrhotic subjects and 4 with congestive heart-failure—i.e., in all cases where satisfactory pictures were obtained—is further evidence of the functioning of this anastomotic system.

PAIN

THE possibility of pain appeared when life first began, and the capacity to react to injurious stimuli was the earliest protective mechanism to develop. The power to perceive pain came later with the appearance of a complex nervous system. In the most highly developed animals a great variety of extra- and intra-corporeal stimuli can produce a sensation of pain, and in man, among the internal stimuli, disordered thought and emotion can give rise to sensations of pain alleged to originate in a somatic region. In all ages there have been theories to account for pain, from the primitive idea that it is always inflicted from without, by enemies or spirits, and can be extracted by mechanical or magical means, to the highly philosophical hypotheses of some of the Greeks. Many of the Greek ideas seem remarkably like those of our own times, though in fact a superficial similarity of principle covers a wholly different background of knowledge and speculation. On the other hand, it is possible that the meaning was closer to our own than we think, because though certain words can be translated, the contemporary significance of them has been lost. Not until the anatomy of the nervous system was at least partially known could rational theories on the cause and perception of pain be developed, but we are still unsure of the peripheral and central mechanisms of pain.

As Dr K. D. Keele points out, in a fascinating account[1] of the knowledge, or anatomies, of pain from primitive times to the present day, we are apt to think that only the present or immediate past has made any notable contribution to the problem. It is salutary to realise that Galen believed the sensory and motor nerves to be separate, and that the brain received all sensations. He even performed the experiment of hemisection of the spinal cord and noticed the paralysis on the same side as the section, but failed to notice the contralateral sensory loss. In this field, as in so many, the ideas of Leonardo da Vinci were well in advance of those of his contemporaries.

Despite the great amount of work that has been done in the past 150 years, we are still unable to explain the diversity of pain sensations or to describe many of them, just as we still do not know where and how pain is perceived. As Keele says, there is now a strong tendency to return to the idea of a sensorium commune and say with Harvey that "we do not feel with the same sense by means of which we are conscious we feel ... but by another sense or sensitive organ ... by which we examine those things that reach us through each of the external sensoria."

ANTIBIOTIC PROPHYLAXIS

IN discussing the abuse of antibiotics we have deplored the routine employment of these drugs as prophylactics.[1] More often than not, the belief that antibiotics will prevent bacterial infections is unjustified, and their misuse in this fashion is potentially hazardous. Enumerating what he held to be the legitimate uses of prophylactic antibiotic therapy Garrod[2] pointed out that the suitable occasions are specialised and relatively uncommon. To use antibiotics for clean operations with the object of escaping wound sepsis or respiratory complications is a vain hope, as a gesture it represents lack of confidence by the surgeon in his own or his staff's aseptic technique. Moreover, even when there is a proper indication for antibiotic prophylaxis, it is often impossible to prevent bacterial infection in this way. There is good hope of success in preventing specific infections due to bacteria that are always sensitive to a particular drug—for example, in the successful prevention of group-A hæmolytic streptococcal infection and its complication, rheumatic fever, with penicillin, and of meningococcal infection with sulphonamides. Results are not so good, however, if cover is required against a variety of organisms that may be resistant to the agents used. Pulaski[3] in a recent brief review refers to reports of unsuccessful prophylaxis in these circumstances. Antibiotics failed to prevent bacterial complications in measles and in cases of poliomyelitis with tracheotomy. Among patients undergoing operations on the biliary tract, subtotal gastrectomy, or resection of the colon with anastomosis, postoperative complications were as common in those who received antibiotics as in those who did not, and the incidence of wound infections after appendicectomy for acute suppurative and acute gangrenous appendicitis was not reduced by parenteral tetracycline therapy.

Antibiotics are often prescribed as a prophylactic for unconscious patients, and Petersdorf et al.[4] have evaluated this procedure in a careful study of 72 comatose patients. Unconsciousness was generally the result of a cerebrovascular accident. Some of these patients received antibiotics either singly or in combination, others did not. No benefit was derived from the chemotherapy, on the contrary, patients given antibiotics were more susceptible to pneumonia, cutaneous staphylococcal infections, and bacteræmia due to gram-negative bacilli. Chemoprophylaxis did not reduce nasal or nasopharyngeal carriage of *Staphylococcus aureus*, and the strains isolated from the treated group were more resistant to antibiotics than those cultured from the controls. Replacement of the nasopharyngeal flora by gram-negative bacilli was commoner in those receiving antibiotics. Routine administration of antibiotics did not prevent infection of the bladder in patients with indwelling urethral catheters but often resulted in the infecting organism being a highly resistant proteus or pseudomonas Petersdorf et al concluded that, far from being beneficial, antibiotic prophylaxis in these patients was distinctly risky

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[1] Anatomies of Pain. By K. D. KEELE, M.D., F.R.C.P., consultant physician, Ashford Hospital and Staines Hospital. Oxford: Blackwell Scientific Publications. 1957. Pp. 206. 27s. 6d.

[1] *Lancet*, 1955, i, 1059.
[2] Garrod, L. P. *Brit. med. J.*, 1955, ii, 756.
[3] Pulaski, E. J. *Practitioner*, October, 1957, p. 465.
[4] Petersdorf, R. G., Curtin, J. A., Hoeprich, P. D., Peeler, R. N., Bennett, I. L. *New Engl. J. Med.*, 1957, 257, 1001.

The danger of widespread chemoprophylaxis is not only to the patient himself but also to the hospital community at large, for every patient given antibiotics may become a source of highly resistant organisms In situations where infection is a risk the best policy is one of watchful waiting and vigorous treatment of specific intercurrent infections if they develop But, since prevention still is better than cure, there is also a need for some fresh reviews to be made of the "aseptic regime" as practised in our hospitals, especially in the wards and casualty departments

TOTAL ADRENALECTOMY IN MALIGNANT HYPERTENSION

As long as hypertensive disease remains in the benign phase the physician can afford to take his time in deciding on the best course of treatment, whatever his misgivings about the term "benign" But once the malignant phase is entered, he faces a desperate medical emergency in which every day counts, because the high blood-pressure has now begun to cause renal damage of a kind which will generate secondary hypertension and soon render the disease irreversible If left untreated this process is virtually certain to kill the patient within months On the other hand if the pressure can be reduced early enough and kept under control—not necessarily at a normal level—the malignant process can often be held indefinitely in check

One possible way of doing this is to remove both suprarenal glands But since the adrenal cortex is essential to life, and has complex and poorly understood functions which can be only partly restored by substitution therapy, its total removal cannot be contemplated without misgiving

It is true that the blood-pressure is low in adrenal insufficiency and high in certain rare forms of cortical overactivity in man, and also that the level of experimental renal hypertension can be lowered by adrenalectomy and restored by treatment with cortical extracts These facts and many others leave no room for doubt that the suprarenal cortex plays an important part in the normal control of blood-pressure But so do many other factors, and it would be unwise to conclude from the available evidence that the suprarenal cortex is vitally concerned in the pathogenesis of essential hypertension In these circumstances adrenalectomy must be regarded simply as one of a number of ways of lowering blood-pressure, neither more nor less empirical than administration of hexamethonium or reserpine None of these corrects the essential abnormality of hypertension, and treatment at present is largely a matter of steering an uncertain course between the opposing evils of excessively high pressure on the one hand and excessively low pressure on the other

How has adrenalectomy worked in practice? Professor Melville Arnott and his associates [1] have lately reviewed the published reports on this question Much of the evidence is difficult to assess because commonly adrenalectomy has been subtotal or has been combined with other measures, owing to a proper concern with helping the individual patient rather than answering a general question But with generous allowance for the inadequacy of the data and the serious condition of the patient, the results of adrenalectomy do not make cheerful reading The immediate mortality is disturbingly high, and of the survivors the proportion whose symptoms persist and who die later on is not encouraging Arnott et al felt that a more precise assessment was needed because of the evidence relating the suprarenal to hypertensive disease, which they regard as strong, and they decided to make detailed studies in a limited series of six patients with malignant essential hypertension who had failed to respond satisfactorily or were intolerant to intensive treatment with oral or parenteral antihypertensive drugs Their criteria in assessing response or intolerance are not stated, but severe renal failure was regarded as contraindicating adrenalectomy

After 20–30 days' rest in bed without other treatment, bilateral adrenalectomy was performed under general anæsthesia Cortisone treatment was started the day before operation, the dose being reduced as soon as possible afterwards, and detailed clinical and laboratory observations were continued for many days Of the six patients three died within 8 weeks of the operation one within 36 hours from a precipitous fall in blood-pressure with extensive cerebral damage, a second on the 6th day from ventricular failure following a steep rise of pressure, possibly due to too much cortisone, and the third from a cerebral thrombosis 53 days after the operation The remaining three patients are all alive, two after 2 years and one after 18 months, and in a satisfactory state although signs of mild adrenal deficiency have developed, and a slight increase in the dosage of cortisone quickly recalls a severe hypertensive state

Thus adrenalectomy may, like antihypertensive drugs, reverse the malignant phase in essential hypertension, but, as Arnott et al point out, it should not be undertaken unless medical measures have failed, and it should never be attempted in the presence of frank renal failure At the same time the experience of Arnott et al confirms earlier reports that total adrenalectomy in malignant hypertension is an extremely perilous undertaking which has no specific effect on the underlying hypertensive state, and many physicians may prefer to persevere with vigorous medical treatment

MINOR METAMORPHOSIS

At this New Year we have changed the type in which the text of *The Lancet* is printed Our object is to make it, on the whole, easier to read, without much loss of matter Having waited long but vainly for someone to design a new type which would be both suitable and very modern, we have reverted instead to one of the old masters of typography Christophe Plantin (1514–89) would scarcely recognise the type named after him indeed the original fount is now said to have been cut by Garamond or Granjon But the Monotype version of Plantin which we are now using is both traditional and well proven, having given good service since it was issued in 1913

To those who liked our pages as they were, we are grateful, but we hope that they may in time get used to the new ones Meanwhile they will recognise that occasional metamorphosis is a biological necessity for a journal as for other larval organisms The ultimate imago is beyond our present imagining

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[1] Arnott W M Crooke, A C Donovan, H Taylor, S H *Quart J Med* 1957, 26 50

Special Articles

A DISTRICT MENTAL HEALTH SERVICE

The Worthing Experiment

JOSHUA CARSE
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From Graylingwell Hospital, Chichester

FOR over a century, psychiatric practice in Great Britain has put its emphasis on inpatient treatment, and the public have come to believe that little can be done outside the mental hospital. Up till 1930 there were few outpatient clinics, little encouragement was given to seek early treatment, and positive action was taken only after the illness was fully established and admission under certificate to a mental hospital was unavoidable. Even today, for the great majority of mentally ill patients, treatment still means admission to hospital. The psychiatric units attached to teaching hospitals are primarily intended for teaching and research, and, though outpatient clinics at general hospitals provide some therapy, large numbers and shortage of time oblige them to refer to mental hospitals most of their patients who need treatment. Any mental hospital which cares to examine its records will find that from half to three-quarters of its admissions come from the clinics.

Faced with a continuing increase in the number of admissions, together with serious overcrowding, our mental hospitals will soon be unable to meet the demands made on them. Admissions to designated mental hospitals in England and Wales rose from 55,856 in 1950 to 71,699 in 1954, and to 78,586 in 1955. By 1955 these hospitals were overcrowded to the extent of 17,965 patients. Clearly immediate action is essential if the required treatment is to be given. One solution is build more hospitals, but this, however, is impracticable because of the cost and the difficulty of staffing. A possible alternative is to spread the load by greatly expanding outpatient treatment facilities.

In 1956 the South West Metropolitan Regional Hospital Board, with the financial help of the Nuffield Provincial Hospitals Trust, decided that Graylingwell Hospital should undertake a two-year pilot experiment by providing an outpatient and domiciliary treatment service based on the coast town of Worthing. The service began on Jan. 1, 1957.

The First Ten Months

The area covered extends about 9 miles eastwards, 9 miles westwards, and 8 miles inland, and covers a population of 160,000 people. All patients, except a few sent from the magistrates' courts, are referred to the service by their family doctors. We insist on this because we are convinced that a close and friendly liaison with the patient's own doctor is essential. No patient is admitted to Graylingwell from the Worthing area without being screened by the service, and thus ensures that hospital treatment is reserved for those cases in need of it.

Worthing and district were chosen for this pilot scheme because they are sufficiently remote (22 miles) from the parent hospital, Graylingwell, to show if it is possible to provide psychiatric treatment for large numbers of patients without the immediate availability of the resources of a modern mental hospital. Another reason was the variety of the population. There are people living in busy towns and others in hamlets and villages, some remote and isolated. There are retired, professional, business, industrial, and agricultural classes. Worthing itself has one of the highest proportions of elderly people of any town in England or Wales, and how far it is possible to treat as outpatients the aged who become psychiatrically ill is a matter of urgent concern to us.

The headquarters of the service are housed in a 20-bed unit, already belonging to Graylingwell, which is now also used as an active treatment centre and day hospital. There are no resident patients.

Working in the service are two full-time and one part-time psychiatrists (five half-days per week). There is always one trained psychiatric sister living at the treatment centre, and during weekdays there are also two staff nurses and two ward orderlies. Staff for the treatment of male patients is supplied from Graylingwell by the chief male nurse who, with the matron and their senior staff, visit the centre periodically. The social work is done by one psychiatric social worker and one hospital almoner. Occupational therapy is organised and supervised by one senior occupational therapist. The secretarial work is done by one medical secretary with part-time clerical help (four half-days per week) supplied by the hospital.

The Patients

In the first ten months the service dealt with 1192 patients (376 men and 816 women) of whom 1110 were new cases. The other 82 were patients who had had psychiatric treatment before Jan. 1, 1957, and are now receiving follow-up supervision and treatment through the Worthing service. 318 of the patients were sixty-five years of age or over.

The psychiatric outpatient clinic of Worthing Hospital is included in the service and 421 patients were seen there. This close link with a general hospital has already proved of great advantage. 339 patients were seen by appointment at the treatment centre. This part of the service is much appreciated by the family doctors because the patients are examined and a report sent promptly and there is no need to wait for a vacancy at the clinic.

Treatment

Over 1000 domiciliary visits were paid by the psychiatrists to 432 patients. Often more than one visit is necessary, and with the assistance of the social worker we are often able to help the patient and his relatives to sort out difficulties which are largely responsible for the breakdown. This work is exacting and time-consuming, but we believe it is sometimes better psychiatric treatment than to allow the patient to run away from his problems by sending him into hospital. No fee was received for any of these visits.

Patients cannot be effectively treated as outpatients unless extreme care is used in physical treatments. Each of our patients first has a thorough physical examination and a comprehensive laboratory investigation before treatment is begun. These were carried out at the department of pathology at Graylingwell Hospital.

Among the outpatients attending the treatment centre electroconvulsant therapy has been used extensively. The courses are short, averaging only 4.9 treatments. Although this is less than is usually given to inpatients, it has proved adequate and so far few patients have relapsed. As it is not necessary to enter hospital, patients are willing to be treated earlier in their illness and need only this shorter course.

Modified insulin has also been used to good effect in the treatment of tension states. The patients spend the day in the treatment centre, and to avoid complications only a low dosage is used, but the course is lengthened if necessary.

Individual psychotherapy is the main treatment for many patients, and is, of course, given to all patients attending the centre A weekly session of group psychotherapy is also held Details of the treatments given up to Oct 31 are

—	Electrical treatment		Modified insulin		Psychotherapy		Drug abreaction	
	M	F	M	F	M	F	M	F
Patients	68	249	3	163	68	125	3	13
No of Treatments	365	1201	54	1957	309	827	3	26

Effect on Hospital Admissions

The number of admissions to Graylingwell Hospital and Summersdale Hospital (its non-statutory short-stay unit for recoverable patients) from the area served by the Worthing and District Mental Health Service during the first ten months of 1957 fell by 324 (59%), compared with the same period in 1956 (table I) Admissions from the rest of the catchment area of the hospital increased by 23, though 1956 was the year with the highest admission-rate in the history of the hospital, which suggests that the demand for psychiatric treatment is still increasing

TABLE I—ADMISSIONS TO GRAYLINGWELL HOSPITAL AND SUMMERSDALE HOSPITAL

—	1956	1957	Difference
Admissions from catchment area served by Worthing service	548	224	−324 (−*59%*)
Admissions from catchment area *not* served by Worthing service	603	626	+23 (+*4%*)
Total admissions	1151	850	−301 (−*26%*)

At Summersdale Hospital the impact of the scheme has been even greater (table II), the number of admissions fell by 221 (77%) This has not surprised us, for we have become convinced that if outpatient treatment is available these patients need only exceptionally enter hospital On the other hand, the reduction of 40% in the admission-rate to Graylingwell Hospital was unexpected, for this hospital receives the more advanced and acute mentally ill patients, and we were doubtful whether the service could help them much The reduction, however, has been steadily maintained over the ten months and it seems that an outpatient service can treat even these patients where the background is favourable

TABLE II—ANALYSIS OF ADMISSIONS FROM WORTHING AREA

—	Graylingwell Hospital			Summersdale Hospital			Total		
	M	F	T	M	F	T	M	F	T
1956	108	152	260	69	219	288	177	371	548
1957	69	88	157	22	45	67	91	133	224
Reduction	39	64	103	47	174	221	86	238	324
	36%	42%	40%	68%	79%	77%	49%	64%	59%

Elderly patients are especially reluctant to enter hospital and outpatient treatment has proved effective in this important group of patients The number of admissions among elderly patients fell by 55 (51 4%) in 1957 (table III)

The commonest psychiatric illness among these patients is depression. The attack can be severe and often it is the first psychiatric breakdown in a patient with a good stable personality If the condition is diagnosed promptly, suitably modified electrical treatment as an outpatient will bring about a remission But delay in treatment allows time for physical deterioration

TABLE III—ADMISSIONS AMONG ELDERLY PATIENTS

Age	1956	1957	Difference	
65–69	57	20	−37	−55 = 51·4% reduction
70–74	50	32	−18	
75–79	31	18	−13	−24 = 38 7% reduction
80–	31	20	−11	
Total	169	90	−79	= 46 9% reduction

Among patients aged seventy-five and over the admissions fell by 24 (39%), but we adopt a cautious attitude toward this age-group Though the reduction in the admission of elderly patients has been steadily maintained over the past ten months, the admission of senile patients fluctuates widely and the present reduction may be only temporary

Discussion

Our experience at Worthing has convinced us that for a large proportion of psychiatric patients, admission to hospital is unnecessary and outpatient treatment can be entirely effective Indeed, there is much to suggest that our mental hospitals have been carrying an unfair burden by being compelled to treat all types of patients without discrimination It should not be thought, however, that our experience has led us to the conclusion that the mental hospital is an anachronism and redundant indeed our respect for it has increased Now, however, we see it in its true perspective as a hospital for selected patients, mostly with a good prognosis, but needing special treatment and conditions which cannot be provided by an outpatient service

Each of us has had some difficulty in reorienting ourselves to this new form of psychiatric practice We had accepted the idea that it was good for a patient with a mental illness to be removed to the artificial environment of a mental hospital and placed under control before he received treatment In an outpatient treatment service it is never possible to divorce the patient from his family and background, and indeed from his own doctor We ourselves, therefore, have had to make some readjustments

Only a proportion of patients are suitable, and we have come to regard the following basic requirement as essential to successful outpatient treatment

Good Public Relations

The success of a district mental-health service depends on its public having learnt to accept mental illness as it would any other illness and to seek advice and treatment promptly In this respect, West Sussex is probably better off than many other parts of the country For some years frequent talks, followed by visits to the hospital, have been given to many groups of people, and psychiatry and the mental hospital is no longer a mystery Fear of Graylingwell has largely disappeared, as is shown by the fact that of the 1347 patients admitted last year, 85% were either non-statutory or voluntary patients The Worthing service has itself done much already to encourage patients to seek treatment promptly

Cooperative Patients

At the treatment centre and at the clinic we must have full cooperation from the patients Usually this is willingly given, the patient does not want to enter hospital, but he does want treatment Where insight is defective, however, admission to hospital may be necessary if treatment does not quickly bring about noticeable improvement

Favourable Home Background

Our patients are not in hospital under trained observation, but they are at home with their families *Unless the relatives* are prepared to work with us and to accept some responsibility for the patient, the case is unsuitable for outpatient treatment. Usually the relatives are most helpful, but we have to make sure, too, that they themselves are not exposed to unreasonable strain If the pressure becomes too great, the patient must be admitted to hospital

Reasonable Risk

The commonest risk, of course, is that of suicide by a depressed patient. If such a patient is living alone it would be an unreasonable risk to treat him as an outpatient. On the other hand, if there is a favourable background and his history is reassuring, he may well be so treated. Each case must be treated on its own merits, but where there is any real doubt inpatient treatment is necessary.

Risk from a patient acting dangerously towards others is less common, and where such a tendency does exist we advise admission to hospital.

Another risk we have to assess is that arising from the physical condition. A patient may be referred to us suffering from a psychiatric illness which will benefit from treatment, but his physical condition may be such that it would be too risky to treat him as an outpatient.

Effective Range of Treatments

We retain in the Worthing service only those patients who can benefit from the treatments which we are able to offer. In our opinion the clinical results from outpatient treatment are equal to those of hospital treatment. We are unable, however, to provide deep insulin-shock therapy or prefrontal leucotomy and when patients need these forms of treatment we arrange for their immediate admission to hospital.

The medical practitioners have had also to make some readjustments because the procedure for the treatment of psychiatric patients has been changed. Formerly the doctor referred his patient either to the Worthing Hospital outpatient clinic, or, through the duly authorised officer arranged for his immediate admission to hospital. Either way, apart from a psychiatric report, he often lost all personal contact with his patient until he received a second report informing him that the patient was being discharged. Today, for more than half the psychiatric patients in our area, treatment is given on an outpatient basis and the patient remains in the care of his own doctor. In general the new method has been welcomed. The family doctor is now working with the psychiatrist, and, while there must sometimes be difference of opinion, so far we have met no serious difficulties. If a serious difference of opinion should arise, we would leave the final decision to the patient's doctor. We have enjoyed meeting the doctors at the treatment centre or on domiciliary visits, when we are able to have friendly discussions about the diagnosis and treatment of their cases. Though formal reports are still necessary, this constant personal contact with the patient, his family and background, and his own doctor has offered us conditions which make possible the practice of individual psychiatry—the ideal of every psychiatrist.

The effect of the district service on Graylingwell Hospital is already noticeable. The fall in admissions has considerably eased overcrowding. This, we believe, could be entirely removed by the provision of outpatient treatment services in the rest of the hospital's catchment area which is now under consideration.

Conclusion

The Worthing and District Mental Health Service is a two-year pilot experiment. It is essentially a research project, for this service is the first of its kind to be undertaken by a county mental hospital. It has been in operation only ten months. In our opinion, however, we already possess sufficient evidence to prove that such an outpatient service can do much to ease the strain on the mental hospital, and this was the object for which it was designed.

The Worthing service has revealed many aspects of clinical psychiatry which could be the subject of fascinating research for many years to come. Even at this early stage however, it may also be indicating a blueprint for future psychiatric practice: each catchment area will have at its centre an efficient mental hospital, with satellite outpatient treatment services which ensure that only those patients are sent into hospital who really need to be there.

HIGHER EDUCATION IN AUSTRALIA

FROM AN AUSTRALIAN CORRESPONDENT

Since the war, Australia has become one of the most rapidly expanding countries in the world. The population has grown at a rate of 2½% per annum over the past ten years, and there has been an equally startling growth of secondary industry, supported by a steady advance in primary production. At the same time Australia has come to play a much greater part in the political and economic affairs of South East Asia and the world at large. It follows that in the future she will require an increasing supply of university graduates to meet her professional, cultural, and technological needs.

In 1956 Mr Menzies invited a committee, headed by Sir Keith Murray, chairman of the University Grants Committee in Britain, to investigate the position of the Australian universities and to suggest how these could best play their part in the development of the country. This committee's report shows a disquieting situation. Far from being ready to meet the immense future demands upon them, the universities of Australia are evidently tending to stumble under the burden of their present reponsibilities.

DIFFICULTIES OF AUSTRALIAN UNIVERSITIES

Their peculiar difficulties are often insufficiently appreciated outside Australia, and indeed have scarcely been realised by a majority of Australians. There are nine universities and two university colleges. Apart from the postgraduate National University at Canberra, which is a Commonwealth affair, the major universities are primarily the responsibilities of the States in which they operate, and so far New South Wales is the only State which has more than one. It is thus inevitable that regional problems should arise. The economies of the States vary widely, and the facilities and finances of the State universities are far from comparable. Nevertheless, many difficulties are common to all Australian universities, and the committee has considered some of these at length.

The basic problem is the weight of student numbers, particularly in the first year.

The Australian universities have set their faces against any form of pre-selection of students, and in consequence everyone who can pass the matriculation examination is automatically admitted to the first year in the faculty of his choice. The pressure is perhaps greatest in the departments of physics, chemistry, and mathematics, which provide the basis of so many professional curricula, but many arts departments are almost as badly affected.

Where classes are 800 strong and practical work is replicated in six or seven sessions, the individual is necessarily submerged, and it is almost impossible to organise the personal attention which is one of the most important things a university can offer. There is an appallingly high failure-rate in the first year, and the student comes to regard the examination as the chief motivation for his efforts. The attitude so acquired is unfortunately difficult to eradicate in the later stages of his education, when the desperate struggle for survival has abated somewhat.

At some universities very many part-time and external students are enrolled. Because of the awkward requirements of laboratory and practical work, such students are found in greatest numbers in the faculties of arts, where they create special difficulties For example, a great deal of teaching has to be done in the evenings, and lectures and seminars have to be duplicated

Yet the principle of unrestricted entry is deeply ingrained by tradition The previous educational experiences of matriculants are so varied that it is thought essential to give them all a chance under identical conditions before presuming to choose which of them are fitted to continue their education further Indeed, the committee, after considering the situation carefully, did not suggest any modification of this admissions policy

TEACHERS AND BUILDINGS

If student numbers are not restricted, efficient and meaningful education can be provided only where accommodation, equipment, and staffing are adequate, and in these respects the situation appears not only alarming but critical

In most universities "temporary" buildings have been put up in an attempt at expansion, like all temporary buildings they have become permanent in an unpleasant sort of way, and a secondary growth of further "temporary" accommodation has sprung up around them

This situation arises partly because the universities live under an administrative system which does not allow them financial security for more than a year ahead Anything beyond ad-hoc planning is thus a desperate venture Little has been done for many science departments since the day they were first equipped, and laboratories are often woefully ill-matched to the tasks now laid upon them

Even more important is the difficulty of attracting and keeping staff of the requisite high quality, particularly in the sciences The salaries paid are grossly out of line with the corresponding salaries in industry or in such bodies as the Commonwealth Scientific and Industrial Research Organisation, and superannuation conditions in many universities are unsatisfactory Australian universities are also rendered unattractive by their isolation, both from each other and from the rest of the world As the committee point out, Perth is as far from Sydney as London is from Istanbul To make such conditions acceptable to the right sort of candidate it is therefore necessary to have not only competitive salaries and terms of employment but also well-organised and well-financed schemes of study-leave and travel

The lack of adequate staff is one cause of the scarcity of honours and postgraduate students, which is a serious omen for the future Concentration on the pass degree as the chief end of education means that most Australian students of above average ability go elsewhere to complete their honours courses, and are often lost to the country

These disabilities have a readily understandable immediate cause—lack of money Enough money, wisely applied, could transform the situation as regards accommodation and staff The reason for the lack of money is also not hard to discover Quite simply, the average Australian is not preoccupied with education He has as yet little conception of the vital part the universities must play in the economy of his country, and the universities themselves have done little to make the situation clear to the public

With time this lack of interest in the universities will right itself, but time is short If the universities cannot cope with their present problems, how can they deal with the appalling overload they face in ten years' time? In 1967 the university student population is expected to be more than double that of 1957, and the prospect calls for immediate action

RECOMMENDATIONS

The committee have made a number of recommendations designed to remedy the present disabilities and to render the universities fit for their future task

The most important recommendation is the creation of a University Grants Committee on the lines of the British one This would consist of a full-time chairman and seven part time members and would function as an informal body without legislated status Two members would be drawn from the professions or industry, and the remaining five would be academic members covering the five main groupings of arts, social sciences, pure sciences, applied sciences, and medicine and dentistry Grants for recurrent expenditure would be made triennially, and would not be earmarked for particular purposes On the other hand, non-recurrent grants would be given annually, and for specific purposes only

The committee have recommended an extensive programme of financial first-aid for the next three years, while the University Grants Committee is finding its feet They suggest that a total sum of nearly £A12½ million should be devoted to building programmes in the various universities, and that the Commonwealth Government should contribute towards these on an equal financial basis with the States, except that in Western Australia and Tasmania the Commonwealth contribution should be 25s for every £1 spent by the State About another £A1 million should be spent on equipping these buildings, and the Commonwealth Government should contribute 16% of this sum An immediate increase in academic salaries is recommended, the rise being at least £A500 for professors and corresponding amounts for other posts There should be an examination of the conditions of service to see how these might be made more attractive

The committee recommend the creation of a new university in Melbourne to serve the needs of Victoria This university would contain a medical faculty, which would ease the pressure on the present university and ensure an increased supply of doctors to a State whose medical requirements are said to be far from satisfied The committee also suggest the creation of another medical school in New South Wales, possibly in relation to the New South Wales University of Technology The medical school at Sydney has been dealing with vast numbers for many years, and this plan would undoubtedly help matters, though, as the committee suggest, it might be necessary to change the name of the University of Technology to avoid the implication that its medical graduates are technologists Tasmania submitted a claim that the committee should consider the founding of a third medical school there, but in the opinion of the committee Tasmania cannot afford a medical school until the present disabilities of the university have been put right It did, however, recommend the development there of a faculty of agriculture Tasmania is now the only State without a medical school, for the medical school of the University of Western Australia began operations this year It is to be hoped that the unsatisfied aspirations of potential Tasmanian doctors will be met by the creation of the second medical school in Melbourne

The Commonwealth Government has already accepted these proposals But the detailed planning and development of individual universities is, as Mr Menzies has said, a matter for the States, and these have not yet pronounced on the report It is expected that they will implement at least the building part of the committee's proposals, but clearly this will be of little use unless they also accept the salary increases and the other suggestions about the employment of university staff

This historic report should mark the beginning of a new deal for the Australian universities and of recognition by the average Australian that he has in higher education not only an invaluable tool and a vital safeguard to his country's future, but also a priceless and irreplaceable cultural asset

Points of View

DISAPPOINTMENTS IN DERMATOLOGY*

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Some claim that they can recognise a consultant's specialty at sight, and I am told that the gynæcologist, neurologist, pathologist, and ophthalmologist present little difficulty to the initiated. To identify a solitary dermatologist might be less easy, but on his way to a consultation he can always be recognised by the expression of anxiety on the face of the practitioner who has called him out. My object here is to examine some of the reasons for this unhappy state of affairs, and to illustrate them from a few everyday problems

* * *

The first skin clinic I attended as a student—it was also the last—was puzzling I recollect a kindly physician who fingered the most alarming lesions, and then ran his hands over his face and through his hair These lesions bore incomprehensible names, and so did the remedies applied to them, my pathology and pharmacology textbooks had not mentioned them One particularly nasty sight was recommended to me thus "Take a good look at this, you'll never see another" This seemed strange, I was even more puzzled when the next patient proved to have the same disease

The outbreak of war brought these undergraduate studies to a premature close; but I still remember the frustration of those few hours, and many of us must have had a similar experience which has determined our subsequent attitude to the whole subject It has made us view dermatology as a study apart from the rest of medicine having neither pathology nor therapy, beginning nor end.

An eminent pathologist has defined a hæmatologist as a man who makes a living by applying a series of different names to a succession of identical blue globules An existence spent in the dubious differentiation of a succession of identical pink papules is all that is accorded in many circles to the dermatologist. Yet in most skin diseases, a careful history, a careful examination, and a considered diagnosis are as vital as in the rest of medicine

Samuel Butler said that life is the art of drawing sufficient conclusions from insufficient premises but there is no point in neglecting our premises altogether The careful history and examination are never wasted, even if they do not give the answer, and you have to refer the patient to a dermatologist who makes a diagnosis of Pityriasis Lichenoides et varioliformis Acuta, your attention will have assured the patient that you are interested in him, and will give him confidence while you see him through the course of this disease, which may last for months, is not influenced by treatment, and is of unknown ætiology

* * *

Let us imagine that we are confronted by a patient with a rash. At sight we can make a diagnosis of eczema, which statistically is bound to be correct nine times out of ten, or of dermatitis, which is the same thing for all practical purposes except in a court of law But before we can attempt to treat the patient we must make an ætiological diagnosis too

Here lies one of the difficulties on the hands it might look the same, whether caused by 'Dettol,' diesel oil, 'Distaquaine' or divorce, on the face almost identical appearances may be given by sensitivity to cosmetics, chrome salts, or just conscience. Moreover, there may be multiple factors, a nurse may not show her sensitivity to streptomycin until she has some emotional upset, and her cure will involve mental readjustment as well as avoidance of the offending drug But a clinical and environmental history will usually sort out these possibilities, for instance, sudden relapses and good remissions, particularly on exposed parts, point to contact dermatitis, perhaps from cosmetics or other chemicals, a chronic course, especially with a family history of eczema, asthma, or hayfever, makes one suspect a constitutional eczema.

Remember that it is not necessarily an expression of defeat to diagnose constitutional eczema· the diagnosis is often made for sound reasons, in the same way as one detects a constitutional asthma And just as one tells an asthmatic to avoid murky and dusty atmospheres, so one may ask people with inborn eczema to avoid wet or dirty employment without meaning that their eczema was initiated by such work.

Now comes the next cause of disappointment. we have obtained a fair idea of the diagnosis from the history and appearance of the presenting lesion we become bold, and neglect to make a thorough examination of the patient. This is a very risky short cut. For example it can be very humiliating to have your case of "? varicose eczema with œdema" returned to you for treatment of his heart-failure.

Sometimes the patient makes mistakes—often deliberate—about the distribution of his lesions, or he may fail to mention that patch of psoriasis on his abdomen which would give us the clue to his extremely scurfy scalp, or he may be satisfied in his own mind that his broad syphilitic condylomata are really piles, and that this is neither the time nor the place to discuss anything except his distressing and abrupt loss of hair Or perhaps the old lady may be concealing huge chronic leg ulcers, they are being treated by her kindly neighbour with some penicillin cream, so that what presents to you as an eczema of the face is really a sensitisation-eruption

Here I should like to pause for a while to consider the phenomenon of sensitisation, or allergy if you prefer it, as applied to the skin. It is easy to understand how a chemical such as caustic soda or turpentine can cause inflammation after only one or two contacts This is called primary irritation, it is easily recognised, easily avoided, and often correctly diagnosed by the patient.

But the idea of secondary irritation, or sensitisation, is much more difficult

In this case we are dealing with a comparable inflammatory response, but it is one which appears only after repeated contact with something which is not necessarily a primary irritant, even in heavy concentrations The acute eczema which may result from repeated contact with primulas is one of the most familiar examples of this, but the number of potential sensitisers is almost infinite They may be very hard to suspect, for the patient, once sensitised, may react to minute concentrations, and the cause may be some old and trusted friend such as a cosmetic which was thought to be vital to the continued integrity of the skin. I have heard quoted the case of a lady who developed patches of intractable eczema over the face and sternum, she was known to be sensitive to black hair dyes, but all attempts at ætiological diagnosis were foiled until it was observed that one of her male friends had a suspiciously black moustache.

Most of the remarks I have made so far apply with particular force to the difficulty of diagnosing occupational eczema; but I think the frustration which most of us have experienced in dealing with occupational dermatitis merits rather special examination

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* Based on a paper read to the North Gloucestershire branch of the British Medical Association, in April, 1956

The problem is complicated by its relationship with the Law For reasons which are no longer valid, a man disabled by eczema gets more sick pay if it is attributed to his work than if it is idiopathic To decide which it shall be is almost as difficult as to use the McNaughten rules, and the effects of the decision may be almost as disabling, even if somewhat less spectacular

It is a curious paradox that the more sane a murderer appears to be, the greater is everyone's wish to prove him mad so that he may escape the worst penalties In the same contrary manner, the more chronic and disabling, and hence the more idiopathic, the patient's dermatosis, the greater is everyone's *natural desire to call it occupational*, and thus to mitigate his poverty But its persistence through months or years of idleness is really one of the strongest possible pieces of evidence against its occupational origin

I do not deny that true cases of dermatitis from primary or secondary irritants arise in industry these are comparatively easy to recognise, and to confirm by patch testing they subside soon after the patient stops work, and do not return when he goes back to work away from the suspected chemical But unfortunately such cases are a minority, in the majority of those that I see, all the medical probability is against an occupational cause, *and in favour of a constitutional origin*, with or without a psychological overlay But medical probability is a very different thing from legal possibility, and where the possibility exists, we incline to give our patient the so-called benefit of the doubt and to allow him his compensation The position is especially difficult where a constitutional predisposition seems to have been touched off by an occupational factor

The subsequent history of such patients can be very depressing Their eczema, being wholly or largely constitutional, might in any case persist for a long time, their natural desire to blame somebody for it is focused by our certificate on to their employers, and some degree of neurosis is almost bound to develop, especially in those who are maladjusted, or unhappy at home or in their work

In such cases a solicitor may be consulted at this stage, and *the probable results are so well known to most of us that they* need no further elaboration The dreary medical examinations, the dreary days in court, the expert witness obliged to admit that the dermatosis might be attributable to the occupation, and the final state of pensionable unemployability and pruritus, would all have inspired Dickens to great heights, if only the compensation laws had reached their present pitch of perfection in his day

It is therefore unfortunate that, as the Law stands, we may well be forced into certifying that the patient has a legal possibility, against the weight of the medical evidence We may have to do it, but we should realise what we are doing, and try to make it clear to the patient and his relatives

In the long run, the only way out of this difficulty is to get the compensation rates altered—to abolish the illogical difference between the rates for sickness and occupational dermatitis Cases of genuine occupational dermatitis could then be determined on reasonable medical grounds , they should be made notifiable to the factory inspectors or public-health authorities, whose duty it would be to investigate the working conditions, with the *dermatologist's help* if required, and to advise suitable precautions to prevent similar cases The patient's right to a common-law action on the grounds of negligence would remain unchanged, but there would be fewer initial stimuli to such an action The money saved could be devoted to retraining eczematous patients in work where their eczema was not a grave handicap

* * *

But enough of this theorising, practical men such as ourselves want to know what therapy is available Disraeli defined a practical man as one who practises th blunders of his predecessors , and dermatological literature is full of blunders which we can detect in the light of modern knowledge They nearly all have one facto in common—namely, overtreatment

An example of heroic treatment, which no doubt seemed perfectly reasonable when it was suggested, is contained in Radcliffe Crocker's *Textbook of Diseases of the Skin*, in recommending the use of thyroid extract in psoriasis, he writes

> "The dose should not be more than five grains a day *to begin with*, which in a week may be increased to ten grains and in a fortnight to fifteen grains *if* it is well borne, five grain tabloids are the mos convenient form of giving it The risk of disagreeable symptoms is out of proportion to the advantage of taking larger doses, which should never be given unless the patient is in bed and under supervision Bramwell, however, got up to forty tabloids a day Headache, sleeplessness or giddiness, and the pulse rising over a 100, should be the signal to stop it or to diminish the dose Patients get thinner while taking it Less frequent symptoms are nausea, vomiting, failure of breath, diarrhœa, and general rheumatic pains "

That was in 1905, but the contemporary scene gives little cause for complacency, and the road we have travelled over the past few years is strewn with discarded remedies, some harmful, some harmless, and nearly all very expensive Yet we continue to believe in miracles when rest and other *inoffensive remedies are far more likely to be successful*

In this realm many of our disappointments are the result of a mutual misunderstanding between ourselves and the drug firms When introducing a new therapeutic substance to the profession in general, it is occasionally possible for the manufacturer to cite reports of full convincing trials taken from the pages of a reputable journal, it is reasonable for such a drug to be brought to the practitioner's notice, and little harm follows provided that the possible toxic effects are emphasised to him But often *the samples dispensed and the literature provided should* imply no more than an invitation to practitioners to cooperate in a careful clinical trial, and to use new remedies from the makers on any other basis would do discredit to the outpatient department of an animal hospital In dermatology it is the cause of many sensitisation reactions and of much disappointment to all concerned

It happens for two reasons the first is that we may not have time to demand to see full reports of thorough clinical trials which may or may not have been performed the second is that our patients with eczema include a high proportion of chronic cases They are abnormally likely to react swiftly and unfavourably to local applications, they are the type of patient who is unlikely to have been included in a short clinical trial Patients with chronic eczema are not necessarily curable it is not kind to give them repeated disappointments, it is less than *kind to give them repeated attacks* of contact eczema, which can only make them worse in the long run

Virtually all the true contact eczemas are *self-limiting*, and many other forms of eczema tend to undergo spontaneous improvement if the patient can have physical and mental rest One of the commonest disappointments arises from neglect of this fact, we try to take short cuts Rest in bed, oily or watery calamine to taste, and heav sedation if necessary, are far more effective than an uncontrolled resort to the remedies on our *blotting-paper* The skin cannot be bludgeoned into healing, even by hydrocortisone it is a very mischievous animal—*when it is attacked*, it defends itself A skin which has produced an eczema is already in a state of turmoil, it is very likely to become sensitised to almost any local application, and must be treated with the utmost respect

* * *

One of the most urgent symptoms in dermatology is hing, and the preparations which claim to relieve this mptom give us many disappointments The antiuritics of the -caine group are some of the most noxious nchocaine, amethocaine, benzocaine, and a number of milar substances have no place as local applications in zema, they are potent sensitisers, and they distract tention from the fundamentals of treatment, if by any ance they should appear to give temporary relief

In the same category come the anti-histamine ointents, which have no curative effect on the eczemas, and hose antipruritic action should be reserved for insect tes They are only weak antipruritics but they are werful sensitisers

If a patient's itch is severe enough to demand these cal antipruritics, then what he really needs is rest and dation, if he gets unduly clamorous, then it is possible at he is mentally ill and that he needs expert psychiatric well as physical treatment The really bad case of zema, with gross œdema, generalised weeping, and vere exfoliation, is fortunately becoming rarer now at syphilis is being treated without arsenic, and gold being recognised by the rheumatologists as one of the aser metals, but such patients can usually be relieved ramatically by the use of systemic cortisone or corticorophin I mention this parenthetically, lest anyone hould think that I am advocating a policy of masterly nactivity, even in these severe cases , their active treatnent is anything but disappointing

The administration of anti-histamines by mouth calls or some consideration, for it has been strongly advocated n the eczemas

One may say at once that it does not fall into the same reprehensible category as the topical application of the same substances, but unfortunately the anti-histamines have no specific effect on eczemas however they are given Their sedative action may be useful, but similar effects can be obtained at a fraction of the cost by the use of barbiturates, chloral, or bromides In this connection it is worth noting that quite heroic doses of sedative may be needed for instance, a husky man or hysterical woman with eczema can often take sodium barbitone gr 10–15, or a corresponding dose of amylobarbitone, four or five times daily for some days before severe drowsiness supervenes

At this point many will register strong disagreement they have seen dramatic relief from the oral use of anti-histamines in eczema I agree with this, it comes about in this way eczematous people tend to have other allergic diseases, including urticaria, the wealing in urticaria can often be produced by damage to the skin, so a potentially urticarial subject who gets eczema may also have an urticaria, brought forth by each eczematous lesion, and by scratching Therefore anti-histamines, which we all agree are effective in urticaria, are well worth giving by mouth in this sort of eczema, where we can see wealing

But these are all rather minor details Our patients may disappoint us, and be disappointed, for more general reasons

First and foremost is the fact that skin lesions are visible, therefore more than ordinary powers of persuasion are needed to delude the patient into thinking he is cured if he isn't Moreover, it is impossible to prevent his relatives, neighbours, and factory ambulance man from trying their hand at treatment, which makes our task very difficult

Acting in the part of Cleopatra, Sarah Bernhardt stabbed the slave who bore to her the tidings of Mark Antony's defeat at Actium, she stormed, raved, wrecked some of the scenery in her frenzy, and finally, as the curtain fell, dropped in a shuddering convulsive heap As the applause died, a middle-aged British matron was heard to say to her neighbour "How different, how very different from the home life of our own dear Queen" It is well to remember that the patient's life is different from ours he has not seen many dermatoses, and he and his friends fear them all In virtually every case of eczema one must give an assurance that it is not infectious, and that it must not be subjected to homely therapeutic trials, and sometimes one should say specifically that it is nobody's fault, or even that it is not a venereal disease These small assurances may save us from the frustration of attending a patient who seems to fear us what he really fears is that we may have discovered something about his past, and that we won't tell him

Lastly, unlike the general physicians, when we have failed to cure our patient, we cannot hand him to the surgeons for removal of the offending organ with the confident, cheerful, and very truthful assurance that he will be made worse before he is better

It is often asserted that skin patients never get better, that they never die, and that the dermatologist never gets up at night In defence of my craft, I can only plead that we have no monopoly of incurable patients, and that their immortality must do us credit Getting up at night we regard only as a distressing symptom needing skilled investigation we are proud and thankful that we do not suffer from it

I am very grateful to Dr H J Wallace and to the late Dr J M Ellis for invaluable help in the preparation of this paper

Conferences

LIVER DISEASE

THE annual meeting of the American Association for the Study of Liver Disease was held in Chicago on Oct 31, with Dr G KLATSKIN (Yale) in the chair

Acute Hepatic Necrosis

Prof HEINZ KALK (Kassel, Germany) described a biopsy study begun in 1923 The first needle biopsy was made in 1934, and since then 4134 had been done, mostly under direct vision More recently the liver had been photographed through the peritoneoscope Professor Kalk emphasised the advantage of biopsy under direct visual control, blind biopsy might miss patchy or localised lesions

He had seen more than 90 patients in hepatic coma Most of them, unlike those in American and most British series, had acute hepatic necrosis, in 3 rather unusual cases, studied two, four, and six weeks after an episode of coma, the liver was normal On the other hand he had also seen some patients whose livers showed scars of a preceding necrosis, but who gave no history of such an illness, this patchy scarring might easily be missed by blind biopsy Such " scar " or " potato " liver was often associated with normal liver-function tests These " scar " livers he believed to be clinically distinguishable from " cirrhosis ", but by biopsy alone the distinction was not always easy In the acute stage of necrosis the liver was red and swollen with a rounded edge, later, scars appeared and in time became pale and shrunken, the surrounding liver remaining brownish In his experience the left lobe was almost always more severely affected than the right, after recovery the right lobe might hypertrophy and overgrow an atrophic left lobe In time necrotic tissue was replaced by non-specific granulation tissue, scarring resulted if the reticulin framework was destroyed, as the lobular architecture could not be replaced Fibroblasts were then replaced by "scar" tissue, and the deeply grooved " potato ", or " scar ", liver resulted

Once the episode of acute necrosis was past the prognosis was good, though transitory ascites might arise at four to six weeks The real danger facing these patients was not progressive liver-failure but portal hypertension, fortunately they were particularly suitable for shunt surgery In some patients a mixed lesion of " scar liver and cirrhosis " developed, and in these the prognosis was bad, the common end-result being hepatic coma

Some patients had repeated small episodes of necrosis and scarring, leading to a final picture almost indistinguishable from Laennec's cirrhosis In cirrhosis, however, he believed that the initial lesion was inflammation of the supporting-tissue at the periphery of the lobules, leading to secondary death of the parenchymal cells and a uniform, fine granulation In acute necrosis, on the other hand, the primary lesion was death of the parenchymal cells in the centre of the liver lobules, followed by secondary scarring

Cholestatic Jaundice

Dr F W Hoffbauer (Minneapolis) suggested that there could be no hard-and-fast rule as to whether cholangiography was necessary in the diagnosis of intrahepatic cholestatic jaundice (I H C J) If surgical assistance was decided on, he favoured a very limited incision under local anæsthesia, and cholangiography A decision whether or not to proceed to laparotomy should be made in the light of the radiographic findings Biopsy specimens must be taken from the liver at the beginning, not the end, of operation to avoid the histological appearance of " retractor hepatitis "

Secretion of Bile

Dr R W Brauer (San Francisco) believed that bile was actively secreted by the parenchymal cells of the liver The concentration of electrolytes was about the same in the bile as in the blood, but the concentration of bile-pigments and bile-salts was much greater in the bile than in the blood, and there were also more complicated molecules present, such as alkaline phosphatase and mucins The bile canaliculi, he considered, did not behave like the renal tubules—i e , they did not concentrate or actively secrete into the bile—but they did permit equilibration between capillary blood and bile so that small molecules such as water, salts, and glucose could move freely from bile to blood or in the reverse direction Dr Brauer concluded that in I H C J the primary lesion was in the membrane dividing the liver-cells from the bile canaliculi Differential diagnosis from main-duct obstruction was difficult

Dr H E MacMahon (Boston) thought that a definition of I H C J must include all cases with jaundice with no mechanical obstruction of the main bile-ducts and no active hepatic necrosis, and should exclude cases of Laennec's cirrhosis This was not a disease entity but a syndrome comprising different conditions Histologically there were two distinct stages at first the bile-ducts proliferated, later they tended to become scarce and might even disappear altogether, as he had seen following the administration of chlorpromazine The histological picture of I H C J could result from main-duct obstruction, besides cholangitis, cholangiolitis (or primary biliary cirrhosis), acholangitic jaundice, fibroxanthomatous jaundice, mucoviscidosis, occasionally carcinomatous and Laennec's cirrhosis, and hæmachromatosis Clearly the histological diagnosis was difficult and could not be made by the pathologist alone

Professor Kalk said that in the initial stages of I H C J inflammation was conspicuously absent, and he preferred to call the condition a hepatosis

Bile-duct Atresia

Dr R C Harris (New York) had studied by serial biopsy 7 patients with intrahepatic bile-duct atresia At birth the atresia was not complete, but by 2 years all bile-ducts had disappeared Clinically these 7 cases fell into two groups In 4 the course was of long-continued obstructive jaundice, and hypersplenism developed The other 3 cases were more typical of cholangiolitis, and the blood-cholesterol levels were very high Histologically there was little fibrous tissue in the portal tracts This was either a disease of the ductules or possibly a metabolic error, perhaps similar to galactosæmia

Aldosterone in Cirrhosis

Dr J M Stormont, Dr S J Wolfe, Dr B Fast, Dr J Crabbe, and Dr C S Davidson (Boston) had found that patients with cirrhosis had a high urinary excretion of aldosterone compared with normals, but not higher than normals on a low-sodium diet Amphenone was given in an attempt to inhibit aldosterone secretion This drug produced mental changes similar to those in impending hepatic coma, but did not reproduce the typical electroencephalographic changes Some protection against this side-effect was obtained by the simultaneous administration of prednisone In 2 out of 4 patients the secretion of aldosterone was blocked, with consequent sodium diuresis, the other 2 patients did not respond, suggesting that other factors were involved in sodium retention in hepatic cirrhosis

Hepatosplenography

Dr J G Teplick and Dr J E Berk (Philadelphia) discussed attempts to find a non-toxic medium for hepatosplenography Barium sulphate given intravenously to rabbits and dogs outlined the liver and spleen clearly in two hours but could be readily detected in the reticulo-endothelial cells eighteen months later Iodised oil 45%, emulsified in water with 'Tween 80', was also given intravenously to laboratory animals, this outlined the liver and spleen in about two hours and was clearing by five days Toxic reactions were observed, though these were mostly minor and transient If a smaller particle emulsion (10–100 μ) could be prepared this might be a safe contrast medium for intravenous use

Portal Hypertension

Dr C M Leevy and Dr M L Gleidman (Jersey City) had studied patients with portal hypertension by means of liver biopsy and measurement of the wedged hepatic-vein pressure before and after medical treatment Portal hypertension arising in the course of hepatitis and fatty liver responded rapidly, and œsophageal varices regressed as fat was mobilised from the liver Corresponding with this there was an increase in the hepatic blood-flow In patients with active cirrhosis the pressure might fall to normal and varices disappear, but not all patients showed this improvement and those who did not should be offered a portacaval shunt

Wilson's Disease

Dr J M Walshe and Mr S B Osborn (London) reported their work with radioactive copper in Wilson's disease Their results showed that penicillamine mobilised copper more powerfully than dimercaprol, that a normal person concentrated copper in the liver faster than patients with Wilson's disease, and that the specific activity of the urine copper fell sharply in the normal about the time cœruloplasmin-bound copper appeared in the circulation

Dr I H Scheinberg (New York) agreed that penicillamine was an extremely powerful " decoppering " agent, but its activity appeared to fall off after several months of continuous administration He had treated 4 patients with it for nearly a year, and 2 had done well

Liver-function Tests

Dr G M Mindrum and Dr H I Glueck (Cincinnati) reported that in most patients with cirrhosis and many with hepatitis the concentrations of factors V and VII were reduced, even when the prothrombin level, estimated by the one-stage method, was normal In patients with severe cirrhosis and, temporarily, in patients with hepatitis the prothrombin level was often less than 50% of normal and did not respond to parenteral vitamin K Using a two-stage assay for measuring " true " prothrombin, these workers found that this was an excellent prognostic test, especially if the two-hour response to vitamin K was measured The test was not influenced by variations in the levels of factors V and VII

Dr K S Henley, Dr H S Wiggins, Prof H M Pollard, and Dr E Dullaert (Ann Arbor) had estimated the transaminase content of parenchymal liver-cells They made a suspension of parenchymal cells in citrate and estimated the levels of glutamic-oxaloacetic transaminase (G O T) and glutamic-pyruvic transaminase (G.P.T.). They found that the G.O.T. was mostly retained in the cells, while G.P.T. escaped into the suspending medium. This correlated well with the clinical observation that estimation of G.P.T. was a better index of liver injury than estimation of G.O.T.

Dr C. L. STERKEL, Dr J. A. SPENCER, Dr S. K. WOLFSON, and Dr H. G. WILLIAMS-ASHMAN (Chicago) had studied serum-isocitric-dehydrogenase (I.C.D.) levels in patients with liver disease and compared these with serum levels of G.P.T. and lactic dehydrogenase (L.D.). In patients with acute hepatitis, the serum-I.C.D. was much increased; this increase was not found in other forms of hepatic disease except cases of extensive carcinomatous infiltration of the liver. With recovery the serum-I.C.D. returned to normal. The serum levels of L.D. followed no such consistent pattern. The G.P.T. was also increased in acute hepatitis only, and returned to normal with recovery. The advantage of the I.C.D. determination was that it was easier and more specific for liver damage; the level had proved to be normal in 250 other patients with a wide variety of disease-states.

Medicine and the Law

The N.H.S. Tribunal

SOME interesting, and on the whole encouraging, facts are given in the report of the chairman of the National Health Service Tribunal for the three years ending six months ago.

The tribunal's main function is to consider representations that the continued inclusion of a practitioner—i.e., doctor, dentist, chemist, or optician—in the appropriate list would be prejudicial to the efficiency of the service. It also has the secondary function of considering applications for reinstatement.

During the three years 13 new cases arose in which it was asked to direct the removal of a practitioner from the appropriate list, and all 13 requests came from executive councils. In addition, it received 8 applications for reinstatement. This total of 21 cases compares with 33 for the period 1948–51 and 29 in 1951–54.

The total number of cases actually dealt with by the tribunal in 1954–57 was 23: some had been carried forward from the previous triennium, and some had not been finally disposed of by July 4, 1957. In 6 cases, the tribunal directed the removal of the practitioner's name from the list, but in 5 others the case was withdrawn on the practitioner undertaking not to practise under the N.H.S. There was only one appeal to the Minister, and that failed.

The 6 cases in which the tribunal directed the removal of a practitioner's name included 3 doctors.

The chairman, Sir Reginald Sharpe, Q.C., welcomes two recommendations of the Franks Committee on Administrative Tribunals and Inquiries. These are that the right of the practitioner to appeal from the tribunal to the Minister should be abolished, and that the appeal from the decision of the executive council in minor cases should lie to the tribunal instead of to the Minister as at present. This latter recommendation, if put into effect, will much increase the tribunal's work: between 1950 and 1954, the number of appeals from executive councils to the Minister averaged 125 yearly. The addition of this amount of work would clearly make the tribunal much less of a part-time body than at present, but on the whole it seems preferable that such appeals should be dealt with by a properly constituted tribunal with recognised rules of procedure rather than by an official of the Ministry, however capable and impartial.

Sudden Illness and Dangerous Driving

At 10.45 one evening, a man drove his motor-van across a road junction at a fast speed and came into collision with a car. The van then carried on for a short distance and overturned. On a charge of dangerous driving the defendant contended that he became unconscious as a result of being overcome by a sudden illness and that he was not therefore liable at criminal law. The Justices found that the defendant must have exercised skill in driving in order to reach the road junction, but they were of opinion that by the time he reached that point he was not capable of forming any intention as to his manner of driving, and they dismissed the charge. The prosecutor appealed.

The LORD CHIEF JUSTICE, giving judgment, said that the Road Traffic Act, 1930, contained an absolute prohibition against driving dangerously and no question of intention entered into the offence. The Justices probably meant that the defendant was in a state of automatism, but the defendant's evidence was consistent with his being overcome with sleep and falling asleep was not a defence to dangerous driving. There was no evidence that he was suffering from anything amounting to a "blackout" nor that he had ever had such an attack before. Accordingly, the appeal would be allowed.

Mr JUSTICE DEVLIN, agreeing, said that if the onus lay on the defence to produce some evidence of automatism, they had failed to do so, with the result that the Justices had come to a wrong conclusion in law. The defendant had not set up a defence of insanity, and unless there was evidence which showed that his irrationality was due to some cause other than disease of the mind the Justices were not entitled simply to acquit.

Mr JUSTICE PEARSON, agreeing, said that if the defendant was driving at all he was driving dangerously; therefore the question was whether he was driving. Normally, a person in the driving-seat of a car was, prima facie, driving unless there was evidence to show that he was rendered unconscious or otherwise incapacitated from driving the car. For example, the person has an epileptic fit or is reduced to a state of coma or is completely unconscious through the onset of some disease, or he is stunned by a blow on the head by a stone thrown up from the road, or he is attacked by a swarm of bees, so that he is prevented from exercising any directional control over the car. In each case he would not be driving. If a man falls asleep in the driving-seat, after he has fallen asleep he is no longer driving, but at the point at which he is falling asleep he is failing to perform a driver's elementary duty of keeping himself awake and so is driving dangerously. Similarly, if a man knows he is liable to have an epileptic fit, but nevertheless drives, it is a question of fact whether driving, in the circumstances, could be considered dangerous. The answer might depend on the degree and frequency of the epilepsy. Here there was evidence that the defendant was driving, and if the burden of proof was on the defence they failed to prove an extraordinary mischance rendering it impossible for the defendant to control the car or direct its movement.

HILL *v.* BAXTER. *Queen's Bench Division (Divisional Court).* Lord Goddard, C.J., Devlin and Pearson *JJ.*, Dec. 19, 1957. Counsel and solicitors:—Anthony Harmsworth (Sharpe Pritchard and Co., for town clerk, Brighton); John Alliott (Jolly and Co., Brighton).

J. D. PENNINGTON
Barrister-at-Law

In England Now

A Running Commentary by Peripatetic Correspondents

Now is the time for all fat men (and women) to come for the aid of their doctor Having clambered on and off their weighing-machines with wheezings of *horror*, *gastronomic* recidivists occupy most of one's after-Christmas consulting-room space and time decrying the injustice of the Great Scheme of Things

A doctor whose lunch has consisted of answering the telephone through a mouthful of antacid tablets is tempted to be cool with these beach-ball-like malcontents who plough through the menu sideways as well as downwards, and yet swear by all their Metabolites that they eat nothing at mealtimes and less than that in between After these unlikely and interminable affirmations they depart, their toffee-papers *drifting after them like autumn leaves behind a bus, while the* exhausted physician remembers wistfully 'Fatty' Cortez, who, stout as he was, at least stood silent on top of his peak in Darien—if only because he was out of breath

The treatment of such aggrieved and adipose clients varies, because if the doctor is himself dyspeptic or recovering from seasonal roisterings, the patient is liable to collect a diet that would make a hunger-striker feel he was outraging the Sumptuary Laws (More subtle is the prescription of a menu so recherché that an import licence becomes necessary and the foodstuffs so abominably expensive that the patient loses weight worrying how to pay for them) It should be remembered that patients also lose weight if their food is rendered inedible, and it is not difficult to suggest to them an itinerary which includes hotels whose cooperation in this respect can be relied upon

I remember a squadron mess in 1946 where for this reason we all lost considerable weight, and the mess secretary's solution was to engage a civilian who claimed to have been cook to Field-Marshal Montgomery Twenty-four hours and an attack of gastroenteritis later he confessed that *his* Field-Marshal Montgomery was an East Coast trawler

* * *

Now that radio brings its annual deluge of Christmas greetings from all parts of the world, the basic similarity of this great festival in different lands cannot pass unnoticed Certainly, in America, celebrations have a very English flavour You have the same feverish preparations, parties, carols, and traditional turkey This year proved exceptional in only one respect, for the sun shone brilliantly in a still blue sky Against this summer background, it was difficult to accustom oneself to heavily decked Christmas trees But at night, when the soft glow of coloured candles brought warmth and friendliness to hundreds of windows in every street, and the strains of *Good King Wenceslas* could be heard in the distance, the weather no longer seemed to matter

* * *

When, a few days before Christmas, a parcel labelled "football" arrived for Jonathan (aged 10½), I thought it prudent to inspect the contents before passing them on to Santa Claus for delivery My prudence was justified, for the parcel contained an obviously very fine and expensive (association) football in a state of collapse After struggling with and breaking the frayed suture I managed to extract the bladder, in doing so I removed the skin from the backs of three of my fingers and a portion of what appeared to be a collar from the neck of the very special seamless bladder An exciting few minutes were then spent, fruitlessly, trying to inflate the bladder with my car foot-pump Next morning I took the football, bladder and all, to a well-known sports shop in the West End, and asked the muscular young assistant to put it into working order He looked at me with scorn "We don't blow footballs up here, sir," he said "Not even on Christmas Eve?" I asked "No, and you won't get very far with that bladder" Besides a part of the collar, I had removed a section of the bladder wall

When I had bought a new bladder, an adaptor for filling the bladder from a pump, a new suture looking like a bitterminally amputated bootlace, and a large blunt needle for lacing up the latter, I had spent enough for quite a handsome present for Jonathan, but I felt well equipped to cope with the situation Arriving at hospital, I met a younger colleague who a year or so ago had been one of the stalwarts of the United Hospitals soccer team Just the man for the job, I thought, and handed *him the football and my purchases It took him an hour* and a half, with the aid of the laboratory motor pump, to assemble the football ready for use

At 2 a m on Christmas morning I was awakened by a musical tinkling A late carollers' percussion band? No, just the football sailing out of the children's bedroom window

* * *

I rang up the clinic and asked for an urgent appointment for that afternoon The first thing the secretary wanted to know was the patient's name, I countered by saying that I first of all wanted to know if it would be possible for her to be seen that day, *regardless of what her name might be* To this the secretary replied that it all depended on whether or not her surname began with any letter between A and K as they had a new system I could not help but reflect on the marvels of modern medicine when the urgency of a complaint could be influenced by the chance of one's initials

* * *

Quid pro quo is the basis of our relationship with Joe He is our plumber and I look after his dad

The trouble with our house is that four generations of doctors have lived in it The earlier three were either pioneers of the do-it-yourself movement or victims of evolutionary skill in Joe's forebears The trouble with Joe's dad is that corrosion and hard waters have played hell with his own piping systems, which are also of the 1875 vintage Our intercepting trap in the front garden vies with the old boy's prostate for retention symptoms His long-standing hyperpiesia contrasts with the chronic low pressure in our lavatory cistern Joe and I often shake our heads over the imperfection of each other's professional responsibilities Mind you, we do deliver the goods from time to time Ten minutes' work with a set of drain rods or a Higginson syringe can provide thankful relief for both of us Joe's skilful version of an unwanted teddy bear to bring down a leg round the bend made him all square for a similar little job I did for their Elsie It does not pay us to be too critical of the ins and outs of each other's households

Most of our common problems have been physiological, and restoration of function has been our guiding principle—removal of physical obstruction, speeding the circulation, adjusting the pressure on valves and cisterns, soothing the intima, relieving the air-locks and gases, heat-exchange systems, and temperature regulators But physiology cannot take us all the way, and this week anatomy reared its ugly head

Our kitchen range packed up, and my better half wants one of those newfangled stoves put in the opposite corner of the room We handed the place over to Joe, and went to cook snacks over a bunsen in the dispensary Someone was fairly letting fly in the back regions, and then there came a knock on the surgery door Joe requested a domiciliary consultation in the kitchen, so down I went The extent of the laparotomy was more worthy of a necropsy than an operation with a hopeful prognosis The scene was vaguely familiar pipes everywhere, swabs and buckets, overalls and puddles, even to the tea on the trolley Joe was worried about that there big pipe in the middle it did not seem to go nowhere, and maybe only his great-grandad knew where it came from but it was certainly too much in the way in 1957 I suggested radical excision Joe looked horrified, for empiricism was not his line Impatiently I snatched a pickaxe from the floor and buried its point into the lumen of the mystery aorta A trickle of rusty fluid seeped out, but nothing more untoward happened I commanded Joe to cut the section out and hammer up the patent foramina in the wall We have known each other too long for him to disobey, but he gave me a nasty quizzical look If our village gets snowbound again this winter, I doubt if Joe will let me pick up a scalpel to his dad He distrusts my modus operandi

Letters to the Editor

COLITIS FROM GANGLION-BLOCKING DRUGS

SIR,—Kitchin et al [1] refer to diarrhœa as a troublesome complication of treatment of hypertensive patients with mecamylamine This side-effect needs to be stressed because the ganglion-blocking drugs are generally believed to produce constipation, and hence may be overlooked as the cause of diarrhœa Their continued administration may have disastrous results

In the past few years we have encountered three cases of severe diarrhœa and shock in patients treated for a long time with oral pentolinium

The first patient died after operation and at necropsy was found to have a large sloughing ulcer of his cæcum and ascending colon A second patient was found at operation to have a gangrenous cæcitis, which was treated by cæcostomy She recovered after a stormy illness A third patient developed similar features, but began to improve with the prompt cessation of the ganglion-blocking drug and the administration of intravenous fluid and electrolytes Her symptoms recurred after she was given, inadvertently, another dose of the drug She eventually recovered

This severe bowel disturbance was tentatively attributed at first to a high concentration of the ganglion-blocking drug in the bowel, and therefore seemed less likely with a drug which was rapidly and completely absorbed in the upper part of the small bowel, as was presumed to occur with mecamylamine However, there are indications that mecamylamine may also cause colitis

We have recently encountered in a patient under treatment with mecamylamine severe diarrhœa and shock leading to anuria and death At necropsy there was widespread ulceration of the large bowel Another patient taking mecamylamine developed severe diarrhœa which became so bad as to amount to fæcal incontinence This stopped two days after she ceased taking mecamylamine

The ganglion-blocking drugs have now proved their worth in the treatment of severe hypertension, but it is prudent to remember also the dangers of their use and to take these into account, particularly before embarking on treatment of patients with the milder forms of hypertension

A J BARNETT

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SANATORIA BEDS

SIR,—A year has passed since my plea [2] for the preservation of the small sanatoria was published in your correspondence columns

This year has seen a further drop in the number of patients requiring or willing to accept sanatorium treatment for tuberculosis Nowadays admission to sanatorium is rarely indicated A spell of a few weeks following diagnosis to teach the patient how to take the drugs, and see they are tolerated, is useful, particularly with the less intelligent patients Seriously ill patients with tuberculosis are not often seen, but would have to be admitted, as would the homeless, the vagrants, and those who prove too difficult to manage at home

Undoubtedly all these groups of patients are much better handled in small sanatoria than in the large institutions, which tend to have strict rules and regulations that prove irksome to patients who, in the vast majority of cases, feel well Should the rules and regulations be broken the patient may be discharged and refused admission in the future Furthermore, the traditional " dos and donts " taught in these institutions, which have little scientific basis, tend to induce a state of hypochondriasis in certain patients

Surely efforts should now be made to close the large sanatoria which are showing an increasing number of empty beds, but which interested parties and ill-informed administrators strive to maintain Sentiment should be disregarded in this matter, as many of these larger units could be readily adapted as general hospitals or geriatric units, for which the need is so much greater

The more homely atmosphere and less stringent regulations of small units would more than compensate for the possibly slightly increased cost per bed and, furthermore, would prove easier to adapt to the changing needs of tuberculosis

Bournemouth O D BERESFORD

CHEST X-RAY EXAMINATIONS AND RADIATION HAZARDS

SIR,—I have read with interest the article by Dr J B Clark and Dr R Grenville-Mathers (Dec 21) But is it not " straining at a gnat and swallowing a camel " to concern ourselves unduly with the use of chest X-rays for diagnostic purposes in chest clinics whilst patients undergoing treatment by an artificial pneumothorax or, worse, an artificial pneumoperitoneum are subjected weekly for a period of years to fluoroscopic examination involving a dose of radiation greater than that received during almost all diagnostic chest X-rays (excepting, of course, tomography)? All the greater is the alarm when one recalls hearing the advice given casually " Give him a P P " rather than do nothing

Hastings A W ANDERSON

RESPONSE OF MEGALOBLASTIC ANÆMIA TO PREDNISOLONE

SIR,—The article of Dr Doig and his colleagues [1] on the effect of prednisolone in megaloblastic anæmia was of interest, since I have investigated the effect of adrenal corticosteroids on the absorption of vitamin B_{12} in several patients with pernicious anæmia It seemed worth while to evaluate the action of the corticosteroids, since a beneficial effect could explain the spontaneous remissions of pernicious anæmia that have been described [2]

One patient with pernicious anæmia in relapse received 40 mg of prednisone daily for 2 weeks There was no hæmatological response, the bone-marrow remained megaloblastic, and the serum-vitamin-B_{12} level of 0 $\mu\mu$g per ml remained unchanged The fæcal excretion of radioactive ^{60}Co B_{12} in this patient was 98% before prednisone and 86% while receiving prednisone In three additional patients with pernicious anæmia in remission, the fæcal excretion of ^{60}Co B_{12}, compared with control studies, was decreased by 9–12% while receiving corticosteroids

There are several mechanisms by which the corticosteroids might produce a remission of megaloblastic anæmia due to vitamin-B_{12} deficiency—by a direct effect on the bone-marrow, by increasing the secretion of intrinsic factor, or by facilitating the absorption of B_{12} by a presumed non-specific effect on the intestinal mucosa as in the treatment of idiopathic sprue

The decrease in fæcal excretion of radioactive B_{12} found in the patients receiving steroids is small, but may be significant A slight increase in the absorption of vitamin B_{12} could result in the delayed hæmatological response observed by Doig et al Obviously, further studies are necessary to elucidate the action of corticosteroids in megaloblastic anæmia due to vitamin-B_{12} deficiency

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[1] Kitchin, A, Lowther C P, Turner R W D *Lancet*, 1957, ii, 605

[2] Beresford, O D *ibid* 1956, ii 1109

[1] Doig A Girdwood, R. H, Duthie, J J R, Knox, J D E *Lancet*, 1957 ii 966

[2] Bloomfield, A. L. *Stanford med Bull* 1941, 2, 5

University of Louisville
School of Medicine

THOMAS D STEVENSON

INTELLIGENCE OF DRIVERS

SIR,—On each of two recent journeys on the Great North Road I found a large motor-van coming towards me in my lane on a dual carriageway which, though recently opened, was properly marked The lack of perception on the part of their drivers calls to mind the number of drivers of goods, and even public-service, vehicles who failed to reach the standard on psychological tests required by the Army during the late war

Mental subnormality in a driver is a more serious matter than is generally realised At present a mental defective under any form of statutory care is debarred from holding a driving licence—provided he writes "no" in the proper place on a form which has already provided the basis for a satirical sketch on B B C television and is probably as clear to him as an income-tax form is to some of the rest of us Once discharged from statutory care this same defective can apply for his driving licence, and, unless the licensing authority has been informed of the circumstances, get it

It is to be hoped this subject will receive proper attention in the legislation which is to follow the report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency But what of those still dangerously lacking in mental ability who escape the notice of the authorities ?

Northgate and District Hospital,
Morpeth, Northumberland

C GUY MILLMAN

PEPSINOGEN IN URINE AND BLOOD

SIR,—Your annotation (Oct 19) touches many aspects of this fascinating subject and invites comment As one who, you suggest, put forth the claim that uropepsinogen excretion quantitatively reflects gastric pepsin output, may I make a comment ?

The entrance of pepsinogen both into the lumen of the stomach and into the blood, whence it finds its way into the urine, represents only one example of what Dr Hollander and I[1] have elsewhere called the exocrine-endocrine partition of digestive enzymes The evidence regarding this partition ratio was of a statistical nature, but, more important, the evidence was obtained under clearly defined basal conditions This latter point is often overlooked in the by now voluminous literature on the subject

The studies by Hirschowitz et al to which you refer are valuable for exploring the effects of corticotrophin and cortical steroids on this exocrine-endocrine partition Recent work by Rider and colleagues[2] indicates that irradiation of the stomach may alter this partition, and Spiro et al[3] have emphasised the effects on it of inflammatory lesions of the stomach

All these investigations have enlarged the number of variables which must be taken into account, but do not necessitate "complete revision of ideas on the relation of these levels to gastric pepsin output" They cannot invalidate the many articles, some cited in your annotation, which document the clinical usefulness of this measurement

Mount Sinai Hospital,
New York.

HENRY D JANOWITZ

THE REINFORCEMENT OF TENDON-REFLEXES

SIR,—To reinforce, say, an ankle-jerk, ask the patient to hook the fingers of his two hands into each other and tell him that you are about to ask him to pull one hand hard against the other Then say "Are you ready ?" Then, without giving the expected command, strike the Achilles tendon, and you will obtain as much reinforcement as if you had given the command

That is what I was taught years ago, and I have proved the truth of it many times, or at least I think I have Perhaps, relying on clinical impressions, I have deceived myself In the excellent paper by Dr Buller and Dr Dornhorst (Dec 21), it would have been valuable to have fig 3 supplemented by tracings to show the reflex 0 2 or 0 3 seconds after the mere inquiry "Are you ready ?" If reinforcement were demonstrated, it would not invalidate these authors' view of the role of the small motor nerves, but it would, I think, invalidate their statement that there has to be a movement involving effort

London, W 1

JOHN PENMAN

B P AND PROPRIETARY PREPARATIONS

SIR,—*The time is ripe for reassessment of the policy of* the Ministry of Health and Treasury in regard to proprietary medicines The report of the Cohen Committee (which is the basis of official policy) concedes that the pharmaceutical industry has contributed a (comparatively) small *number of outstanding drugs not yet in the B P* Apart from these, everything *B P* is "good enough", and there is no need for manufacturers to introduce "slight variants" (to quote a recent critic) of official remedies

Such an attitude is contrary to the whole course of scientific and industrial advance Progress does not consist only in a few outstanding discoveries, but also in the cumulative effect of a host of small advances and improvements As I have pointed out elsewhere, the motorcar of today does not differ fundamentally from its predecessor of fifty years ago 4-stroke engine, carburettor, clutch, gear-box, transmission, differential, &c But in performance and comfort it has been transformed by constant modification and improvement in detail Similarly in pharmacy Progressive manufacturers are continually seeking to produce "something better" than *B P* They spend large sums, not only on *fundamental research to discover* new drugs, but on formulation research and process research to find better ways of making, using, and combining existing drugs *Modern* drugs are extremely complex and often yield their maximum efficacy only under carefully controlled conditions A wide range of new excipients have been introduced, affording immense scope for experiment and modification The effect of a medicine is not measured by the percentage of the active ingredient The choice of excipient, the physical state of the ingredients, and other factors may materially enhance the drug's therapeutic efficacy To give only one illustration there are no less than three hundred different emulsifying agents at the disposal of the manufacturer from which to select the one best suited to a particular purpose

The Pharmacopœia Commission have not the staff or resources *to do much research* Advances *come* almost invariably from the industry's research laboratories, and may *be reflected in B P standards and* formulations some years later

The existence of standards, whether *B P* or B S I, is a challenge to a manufacturer to go one better, and it would be a bad thing for medicine, for the N H S, and for the export trade if this were not so

It is really time that the *Ministry* and its fellow critics ceased to represent the *B P* as "best possible", and took to heart *the conclusion in Mr J P Martin's* recent book

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1 Janowitz, H D Hollander, F *Gastroenterology* 1951, 17, 591
2 Rider, J A Moeller H C, Althausen, T L, Sheline, G E *Ann intern Med* 1957, 47, 651
3 Spiro, H M, Friedman E, Polner, J J *Clin Res Proc* 1957, 5, 196

Social Aspects of Prescribing that, in selecting proprietary medicines as the principal cause of the high cost of the pharmaceutical service, they are barking up the wrong tree

In a world which is becoming increasingly proprietary-minded the constant denigration by the Ministry of British proprietary medicines may react to the detriment of British exports

Horsham, Sussex. F F MARCHBANK

LEAD POISONING

SIR,—Dr Gillet in his letter of Dec 14, referring to my article of Nov 30, has asked for evidence of the route of entry of the lead

No direct evidence was obtained Ample opportunity for ingestion and inhalation existed Because inhalation is generally regarded as more toxic, this route was considered the more important

Some confirmation of this seems indicated by the fact that the husband and two elder boys who spent little time in the shack presented no evidence of lead absorption, but the wife and younger children who spent more time in the shack did

As far as contamination of food goes, all members of the family would have been at somewhat equal risk

Department of Public Health,
Perth, Western Australia. W S DAVIDSON

CONTROL OF ARTIFICIAL RESPIRATION IN POLIOMYELITIS

SIR,—Dr Walley's paper of Dec 7 raises a number of interesting points in the application of intermittent positive-pressure respiration (I P P.R.) One which has had little attention to date is the interaction, under these conditions, of respiratory factors with metabolic processes in the acid-base balance of the body

Case 1 of Dr Walley's series was clearly in a state of respiratory acidosis due to pulmonary atelectasis This was corrected But the figures cited for blood pH, carbon-dioxide tension, and total carbon dioxide show that the patient then passed, perhaps insidiously, into severe metabolic acidosis Death was stated to have been from anuria

Metabolic acidosis associated with renal failure is by no means an uncommon cause of death among patients undergoing I P P R The factors contributing to it have yet to be fully understood The acidosis may result not only from abnormal metabolic events, such as ketosis in the initial stages of the illness, but also from impairment of the renal mechanisms which sustain the normal pH of the blood.

In conditions which require long-continued artificial respiration an extra burden is imposed on renal function in two ways Firstly, the inevitably increased catabolism of tissue protein requires the excretion of an excess of nitrogenous degradation products This osmotic load may be further reinforced by injudicious feeding with high-protein mixtures Secondly, fixation of the ventilatory volume to a predetermined empirical figure eliminates the partial respiratory compensation which normally follows a metabolic disturbance of the plasma-bicarbonate level [1] Hence there must be increased strain on the renal pH-regulatory mechanisms

The elasticity of renal function may be further reduced by anoxæmia, by toxæmia, and possibly also by changes in the visceral venous blood-flow due to hæmodynamic "back pressure" from the positive endobronchial pressure used for respiration There is some evidence that hepatic function may be modified by this back pressure [2] A high inflating pressure or a shortened expiratory pause, either of which may be needed to maintain an increased respiratory minute volume, results in a raised mean intrathoracic pressure

Disturbances of electrolyte balance can occur in a variety of conditions which may necessitate artificial respiration Suppression of urinary excretion of the sodium and chlorine ions has been described in bulbar poliomyelitis and other intracranial lesions,[3] and of the chlorine ion in tetanus [4] If present, these disturbances add to the complexity of the metabolic picture

Dr Walley has rightly emphasised the importance of blood-gas analysis in the control of long-continued artificial respiration, and in so doing has pointed to other problems

The Poliomyelitis Unit,
Infectious Diseases Hospital,
Portsmouth M W GLOSSOP

PRODUCTION OF FIBRINOLYTIC ACTIVITY WITHIN ARTERIES

SIR,—May we reply briefly to Prof McFadzean's letter of Dec 21?

Firstly, we apologise if our reference to his and his colleagues' work was misleading

Secondly, Professor McFadzean believes that local anæsthesia increases fibrinolytic activity in the vessel from which blood is obtained. In our investigation a local anæsthetic, lignocaine, was used for the arterial punctures, no anæsthetic being used for venepuncture Since we found arterial-blood fibrinolytic activity to be less than venous-blood fibrinolytic activity, we do not see that the second part of Professor McFadzean's letter is relevant to our findings

Finally, we have tested venous-blood fibrinolytic activity with and without lignocaine anæsthesia, and find no difference.

Gloucestershire Royal Hospital,
Gloucester G R FEARNLEY
J FERGUSON

RADIATION AND LEUKÆMIA

SIR,—The report [5] by Court Brown and Doll on "leukæmia and aplastic anæmia in patients irradiated for ankylosing spondylitis" is outstandingly valuable for the estimate that it gives of the increasing incidence of leukæmia with increasing radiation dose in these patients It has in addition, however, been regarded as indicating the probable absence of a threshold for the induction of leukæmia by radiation, despite the authors' warnings that their information on this point was inadequate to justify a definite conclusion

In view of the importance of this subject it would be valuable to have the authors' estimate of their evidence on this question It is obvious that the regression line used in the report is inappropriate to a study of possible thresholds since it is "calculated from the rates for the (various) dosage groups and made to go through the point corresponding to the incidence in the absence of treatment." It would, however, be valuable to know the line of best fit to the points for the irradiated patients only, and so to obtain an estimate for the dosage at which the incidence of leukæmia is no greater than in unirradiated subjects It is clear that such an estimate of a "threshold" may be highly inexact and the confidence limits of the estimate would be helpful in demonstrating this It is clear also that no reliable deduction can be made by the extrapolation of a regression line in this way The need, however, is to assess what inferences as to the likely size or existence of a threshold are indicated, and what are probably excluded, by the observations on which the report is based

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[1] Gamble, J L. Chemical Anatomy, Physiology and Pathology of the Extracellular Fluid. Cambridge, Mass, 1954

[2] Astrup, P, Gøtzsche H., Neukirch F *Brit. med J* 1954, i, 780

[3] Allott, E. N *Lancet*, 1957, i, 246

[4] Glossop, M W, Low, M D W *Brit J Anæsth* 1957, 29, 326

[5] *Spec Rep Ser med Res Coun., Lond* 1957, no 295, see annotation, *Lancet*, 1957, i, 1130

Department of Clinical Research,
University College Hospital Medical School,
London, W C 1
E ERIC POCHIN

NITROUS-OXIDE BYPASS ON ANÆSTHETIC APPARATUS

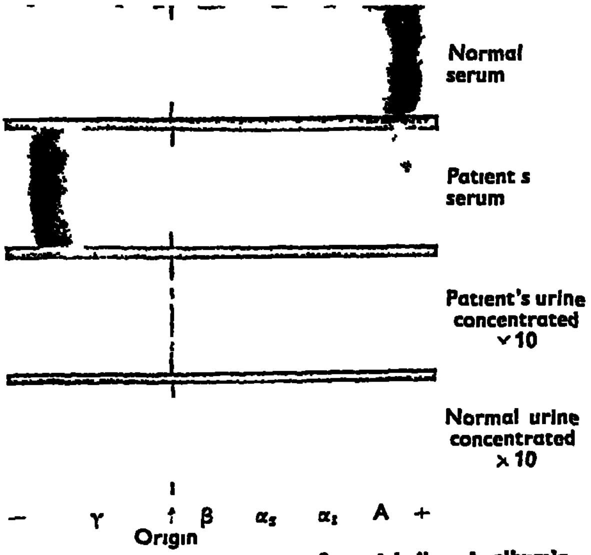
SIR,—There are still numbers of anæsthetic machines in use which have a bypass providing a rapid flow of nitrous oxide as well as one for emergency oxygen The two controls are alike, though at opposite ends of the row of flow-meters It can easily happen in the stress of an emergency that the wrong bypass is opened when it is intended to inflate a patient's lungs with oxygen At least one fatality has been caused in this way I suggest that lives may be saved if every anæsthetist who uses a machine that has a nitrous-oxide bypass takes steps to have it removed

Cambridge
H R YOUNGMAN

UNUSUAL URINE PROTEIN IN *MYELOMATOSIS*

SIR,—Mr Cummings,[1] in describing the urinary-protein electrophoretogram from a case of myelomatosis in which there were three bands in the γ-globulin region, reported that this was the only instance in some 40 cases in which he had found more than one band in this region In Dr Gobert-Jones' case[2] two bands were present in the γ-globulin region

We have recently investigated a patient in whose urine there are apparently four distinct proteins The electrophoretic pattern shows two distinct bands in the region corresponding to the γ-globulins, a fainter one in the region corresponding to the β-globulins, and a fourth which is albumin (see fig)


Normal serum
Patient's serum
Patient's urine concentrated ×10
Normal urine concentrated ×10
−
γ
β
α2
α1
A
+
Origin

Electrophoretograms —α_1, α_2, β, γ-globulins, A, albumin

A man, aged 47, presented with aching limbs and symptoms of anæmia In addition to the urine and serum findings, smears of a marrow aspirate and radiographs were typical of multiple myelomatosis The urines were concentrated ten times by freeze-drying and resolution in *0 05 M* barbitone buffer (pH 8 6) Both the urines (0 05 ml) and sera (0 01 ml) were electrophoresed on Whatman 3 mm paper in a horizontal bath using 0 05 *M* barbitone buffer (pH 8 6) for thirteen hours at a current of 1 2 milliamps per strip

We are at present studying the relative value of different urine tests in differentiating myelomatosis proteinuria from that found in other conditions As an aid to our study we would welcome specimens of urine containing protein from cases of proved or suspected myelomatosis

Department of Medicine,
University of Cambridge
H J WOODLIFF
R W AINSWORTH
R J FLEMANS

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[1] Cummings A J *Lancet* 1957 ii, 598

[2] Gobert-Jones J A *ibid* p 1068

TROPICAL EOSINOPHILIA

SIR,—In their preliminary communication of Sept 7, Dr Gault and Dr Webb reported what appears to be the anterior end of a nematode larva in the liver in a case of tropical eosinophilia, they have also shown gross pathological changes in the liver

It is increasingly being realised that, in tropical eosinophilia, tissues other than the lung are commonly affected Chaudhury,[1] in his series of 167 cases of tropical eosinophilia noted enlargement of the liver in 52 cases, symptoms other than pulmonary (mainly gastrointestinal) in 42, splenomegaly in 14, and enlargement of lymph-nodes in 5 Gupta and Rao[2] have reported eosinophilic nodule of the breast in a case of tropical eosinophilia

The work of Danaraj et al[3] with a filarial complement fixation test, and that of Gault and Webb, strongly support the view that parasitic infection plays an important part in tropical eosinophilia, and that most of these cases are probably of filarial origin Filariasis exhibits itself in a wide variety of diverse and apparently unrelated clinical conditions Apart from the well-recognised clinical features, various other manifestations, such as mastitis, parotitis, thrombophlebitis, rectal bleeding, pruritus, erythematous or papular eruption, have been thought to be due to filarial infection[4] Janssens[5] noted various nervous and psychic manifestations of filariasis This variety of clinical conditions may be explained on the basis of lymphatic blockage and vascular allergy

It seems, therefore, that tropical eosinophilia is just one of the many manifestations of filariasis In spite of the fact that filariasis is so widely prevalent, our knowledge of the disease is woefully deficient

Hasanabad Lane Near Market,
Santacruz, Bombay, 23
B S RAHEJA

A FUNCTIONAL NECESSITY

SIR,—Once again *The Lancet* has advocated the permanent creation of a new grade of hospital doctor intermediate between senior registrar and consultant The letters of Mr Holmes Sellors, Dr Rowland Hill, and Professor Strachan must have made it clear that the representatives and leaders of the consultants are opposed to such a plan I should like you to know that the same is true for the senior registrars and registrars The B M A Hospital Junior Staffs Group (formerly Registrars Group) provides representative machinery to which all members of these grades have access, and the problem of hospital staffing has been our chief concern for the past four and a half years Everywhere and always, the majority opinion has been against a permanent subconsultant grade Of course, there are some now in urgent distress, men around 40 in the major specialties, with higher qualifications, long specialist experience, and satisfactory records who are threatened with dismissal Plans for a subconsultant grade may tempt some of them as a straw tempts a drowning man If a few should even clutch at it, that would not be an argument for providing straws instead of proper lifesaving gear Nor would the fact that straws are cheaper

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[1] Chaudhury R N *J Indian med Ass* 1956 27 195

[2] Gupta I M Rao, M S N *Indian J med Sci* 1957 11 729

[3] Danaraj T J daSilva L S Schacher J F *Proc Alumni Ass Malaya* 1957 10 109

[4] Raheja B S [illegible] (in the press)

[5] *Ann S belge Méd trop* 1952 32, 229 See *J Indian med Ass* 1954 23 269

In considering plans for future hospital staffing much confusion arises unless it is recognised that there are two quite separate problems An immediate solution is needed to mitigate the hardships of the ageing time-expired senior registrar and this must be followed by a long-term solution which will ensure that similar hardships, or others as bad, do not occur again It is absolutely vital that the short-term plan should be consonant with the long-term one, and that the long-term one should be based on serious consideration of what is best for the hospital service, not dictated by the short-term plan To do otherwise is to sacrifice the future to the present.

You do not clearly define the grade of assistant consultant which you propose Evidently it is to be a permanent feature of the service, inferior in status and remuneration to the consultant grade and to offer a career up to retirement in all specialties Immediately, one wonders what work there could be in hospital, suitable for a man over 40 with higher qualifications and long specialist experience which is not consultant work. Dr Rowland Hill says none at all The examples you suggest (presumably the best you could think of) should convince all that he is right

It is widely known that much work which should be carried out by consultants is at present done by senior registrars and even registrars Is it possible to believe that the work allotted to the proposed new grade would be anything less or that the men in the grade would be suitably occupied if it were? It could only be a grade of underpaid, dissatisfied, depressed consultants The financial convenience to the Government of such a grade is obvious Once introduced, nothing could withstand continual pressure from the Treasury to increase the proportion of subconsultants

What then are the correct solutions? As always, close examination of the problem suggests the answer At present, there are too many *senior registrars in the major* specialties in relation to the incidence of consultant vacancies (over 200 each in medicine and surgery compared with an average of 20–30 consultant retirements annually) On the other hand, many senior registrars and registrars are doing work which ought to be done by consultants The correct long-term solution is to create new consultant sessions to cover this work, and discontinue some of the senior registrars' posts thus vacated By these two processes, a proper ratio between the senior registrars and consultants could be established which would allow reasonable prospects of advancement after four years as senior registrar It would also relieve the bottleneck between registrar and senior registrar, and make possible the attainment of a consultant post around 32 years, as envisaged by the Spens Committee

Such an agreement could not be implemented overnight (though there is nothing to prevent the Ministry of Health accepting it in principle forthwith) In the meantime, the present generation of time-expired senior registrars are existing insecurely from year to year on an arrested salary, growing ever older and accepting ever more independent responsibility Their needs as well as their contribution should be recognised by the granting forthwith of security of tenure and a rising incremental scale to those retained after four years This would lift their burden of insecurity, and substantially relieve their financial hardship Yet it in no way interferes with the final solution, or even commits either side as to its nature

ROGER BREARLEY,
Chairman
Liverpool B M.A Hospital Junior Staffs Group

SIR,—The interest taken in your leading article of Nov 30 is further evidence of the urgent need for a satisfactory solution of the problem of hospital medical staffing The S H M O Group of the B M A is profoundly dissatisfied with the present position but is very suspicious of any attempt to create an alternative grade in view of the following grave errors and inherent injustices of the present position

(1) The initial formation of a vague "subconsultant" grade

(2) The expansion which has occurred in spite of the superficially fair document RHB 50/96

(3) The small effect and unbalanced reviews of gradings

(4) The Ministry's continued refusal to allow further reviews

(5) Decreasing possibility of obtaining consultant status

(6) Insidious threat of "clinical supervision" of fully trained staff

For a new grade to be acceptable to S H M O s there would have to be adequate safeguards to prevent a repetition of such past mistakes

All your correspondents have stressed the urgent need for an increase in the consultant establishment, and indeed if the needs of the country in this respect were adequately met the greater part of the problems of the senior registrars and S H M O s might well be solved

The present plight of the senior registrars is desperate and that of the S H M O s is little if any better This state is primarily due to the large amount of consultant work which is being done by these two grades Unofficially this is both well known and is an accepted fact, the time is long overdue for official recognition and action

Certain obstacles have to be overcome to provide a satisfactory solution It is my personal view that ways to do this have evolved from the work of various committees and the efforts of many earnest people The difficulties are as follows

(1) No sudden increase should be made on the country's financial burden

(2) Early selection for permanent consultant status

(3) Adequate and satisfactory opportunities for those who for one reason or another are not so selected

The first step should be to stop creating new senior registrars until the existing ones and S H M O s have been virtually absorbed by the formation of one consultant grade commencing at a salary scale lower than the present consultant minimum (relative), thus avoiding the financial strain of the necessary increase in the present consultant establishment

The salary scale should rise by regular increments to a predetermined level, such as not less than 80% of the present consultant maximum (relative) Attainment of the highest level would depend on responsibility and individual worth Such a solution would affect the present merit-award system in that ability and outstanding merit could be rewarded at all levels for permanent staff

"Supervision" is the cause of much uncertainty and concern, especially as it has never been accurately defined. Fully trained staff on a permanent contract should only be appointed where theoretical knowledge is sound and sufficient experience has been obtained to realise when to take counsel with a senior colleague The administrative division of duties by the senior consultant in a specialty is reasonable and would apply to all specialists in his area, but this would not be supervision of actual clinical work

There should be worth-while alternatives for those registrars for whom there are no available openings when they have finished their trainee period A loss of so much specialist skill would be personally bad and economically unsound

Reorganisation of the public-health and school services could provide a number of attractive posts if liaison with hospital work was developed, and group general practice, as has been so frequently suggested, should be enriched by recruiting from the registrar pool

The present hierarchy who control negotiations on the future of hospital staffing all come from the top end of the consultant ladder and are therefore not acutely aware of the economic difficulties of their juniors Adequate representation of all levels of hospital staff is therefore of paramount importance to obtain a satisfactory solution

Leicester G WARING ROBINSON

UNNECESSARY IRRADIATION IN CHEST RADIOGRAPHY

Mr H FISHER, technical manager of Sierex Ltd, writes

"The article by Mr Clarke[1] refers only to cones for limiting the radiography field No mention is made of the numerous adjustable diaphragms which are on the market, particularly those fitted with a light device for projecting the X-ray field on to the patient Our adjustable light diaphragm, which has come into widespread use in the past years, contains four sets of lead plates which are arranged so as to give optimum cut-off of the X-ray beam The use of such a diaphragm, which also has an accurate light centring device, obviates the need for special precautions—e g, protective screens—for the patient in order to shield the gonads or other vulnerable parts

The cut-off which we can obtain with our diaphragm is equivalent to the cut-off obtained with a lead-rubber sheet as used during normal radiography with a divided cassette, so that the use of such a diaphragm would obviously give optimal radiographic results as well as affording maximum protection to both patient and operator"

Public Health

Statistical Review of England and Wales

IN part I of his Statistical Review for 1956,[2] the Registrar General records the detailed statistics of deaths from all causes and notifications of infectious diseases in that year, by age, sex, area of residence, and time of year

Deaths—The death-rate of 11 7 per 1000 living was the same as that in 1955 The death-rate in the age-group 0–4 was the lowest on record

Stillbirths and infant deaths—The stillbirth-rate remained steady at 23 per 1000 (the rate for every year but one since 1948) The infant-mortality rate fell from 25 per 1000 in the previous year to a new low level of 24 per 1000 The number of deaths from pink disease was 75 in 1947 and 1 in 1956

Cancer—The number of deaths from cancer was 92,710—an increase of 1370 compared with 1955 Deaths from lung cancer increased by 914, the total being 15,615 in men and 2571 in women There were 2315 deaths from leukæmia in 1956, 2224 in 1955, and 1419 in 1946 18% of all deaths were due to cancer

Infectious diseases—There were 5375 deaths from tuberculosis (6492 in 1955), 8 from diphtheria, 15 from scarlet fever, and 30 from measles—all low records There were 114 deaths from acute poliomyelitis

Cardiovascular disease—Arteriosclerotic heart-disease caused 74,790 deaths in 1956, 70,597 in 1955, and 32,487 in 1946 Over 14% of deaths were due to this condition 20,398 deaths were attributed to hypertensive disease, compared with 20,920 in 1955 and 16,757 in 1949

Bronchitis—19,852 men died from bronchitis, the highest figure since the war, except for 1951, the figure for women was 9818

Violence—21,870 (21,460) persons died by violence—5915 (5743) in home accidents, 5236 (5170) in road accidents, and 5282 (5000) by suicide (figures for 1955 in parentheses)

Obituary

THOMAS PEEL DUNHILL

G C V O, C M G, M D Melb, Hon F R C S, F.R.A C S

Sir Thomas Dunhill, consulting surgeon to St Bartholomew's Hospital and sergeant surgeon to King George VI, died on Dec 22 at the age of 81 He was one of the group of distinguished medical immigrants from the Commonwealth who came to practise in this country after service in the first world war His special contribution was to thyroid surgery, and even when the memory of his own technique and dexterity has faded his influence in fostering the study and investigation of the endocrine glands will persist

Dunhill graduated M B with first-class honours from the University of Melbourne in 1904 and was already surgeon to St Vincent's Hospital in Melbourne when war broke out in 1914 He served in France with the Royal Australian Army Medical Corps and before the end of the war he was appointed consulting surgeon to the British Expeditionary Force For these services he was appointed C M G in 1919 His war-time contacts with his British colleagues led to an invitation to join the surgical unit at St Bartholomew's Hospital Soon afterwards he was appointed a full surgeon to the hospital

His first official appointment to the Royal Family was made in 1933 when he was appointed surgeon-in-ordinary to King George V, and in 1939 he became one of the sergeant surgeons to King George VI He was head of the surgeons attached to the Royal Household at the time of the King's illnesses in 1949 and 1951 Dunhill was appointed C V O in 1919, and promoted K C V O in 1933 and G C V O in 1949

Within his own profession and specialty his work was recognised by his appointment to the Arris and Gale lectureship of the Royal College of Surgeons of England in 1931 and again in 1934, and to the Lettsomian lectureship of the Medical Society of London in 1937, and by the award of the society's Fothergill medal in 1941, and the Cecil Joll prize in 1948 He received an honorary M D from the University of Adelaide in 1935, and he was elected to the fellowship of the Australasian college of surgeons the same year and to the honorary fellowship of the English college in 1939 Of the work which had earned these honours J P R writes

Thomas Dunhill's name will live in history because he made outstanding contributions to the surgery of toxic goitre, but those of us who knew him well must recognise that this statement, though true, is but *half*, or even *less than half* the truth

First, it is only part of the truth about the surgery of toxic goitre, for we cannot help thinking of thyroidectomy as it is performed today with all the safeguards provided by pre-operative medication and modern anæsthesia, and there is nothing in the statement to show that Dunhill shortly after becoming qualified realised that, contrary to current teaching, the *illest* patients were the ones who stood most in need of operation, and that he alone had the courage to tackle single-handed and successfully the problem of how to operate on these patients without killing them

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[1] Clarke, W G *Lancet*, 1957, ii, 316

[2] Registrar General's Statistical Review of England and Wales, 1956 Part I Tables, Medical H.M Stationery Office, 1957 Pp 373 15*s*

Nowadays we are familiar with the idea that safety in surgery is a matter of team work, but Dunhill's team consisted of only two people, the patient and himself Recognising the dangers of contemporary anæsthetics he eliminated them by using local anæsthesia For the rest he trusted to gentleness, to knowing when to stop and completing the operation in stages, and to establishing in his patients such confidence that they were prepared to plunge into the deep waters hand-in-hand with him, knowing that he would do his utmost literally to pull them through This amazing story has unfortunately never been told, for Sir Thomas was too sensitive to publish it in his Joll lecture, and it is unlikely that it will ever be told now because Sister Mary Alban of St Vincent's Hospital in Melbourne who helped him with his early operations is an old lady and may not be able to commit her memories to paper It would take too long to go into details, but suffice it to say that Dunhill's pioneer work started in 1906, that he had established his reputation in this branch of surgery long before preoperative iodine became routine in 1923, and that he has been intimately associated with all the advances in the management of toxic goitre since that time

Secondly, the statement is only part of the truth because by concentrating attention on his work on toxic goitre it tempts us to forget his painstaking studies of other aspects of thyroid disease, especially of carcinoma of the thyroid gland, and it is also unjust to him in failing to mention the excellence of his technique in other fields of surgery

He was in the fullest sense of the term a general surgeon, at one time an able gynæcologist, interested and skilled in the treatment of fractures, familiar with the techniques of neurosurgery, and a brilliant exponent of operations such as radical mastectomy and block-dissection of the neck which demanded detailed anatomical knowledge Latterly he confined himself to the surgery of the abdomen and the neck, and made important contributions to the literature on diaphragmatic hernia and pharyngeal diverticulum

Dunhill was always anxious to learn by watching other masters of the craft at work Returning home he would incorporate into his own system anything which he regarded as a technical improvement, and provided that the modification stood up to his critical appraisal, he would accept it as his standard procedure He learned by example, and he taught by example Formal lecturing he dreaded, and his publications, though models of clarity, cost him a stupendous amount of labour Having given so much thought and attention to matters of detail, and having convinced himself that a certain method was the correct one, he was sometimes severe in his criticism of those who through thoughtlessness or ignorance did otherwise, and thus offended against some fundamental principle of surgery To attempt to live up to his high standards has been a stimulus to many a young surgeon, and the generation trained by him will realise that their efforts to perpetuate what they learned from him must be the most worthy tribute to his memory

F R F, describing Dunhill as " a man and a friend ", writes

> He was a big man in many ways He was a skilful and eminent surgeon but that was incidental It was as a man that he was unique, for he developed and used his capacities to the limits of his mental and physical endowment, and gave himself unsparingly to help his fellow men to a happier and a more complete life—not men as a race or a community, but each man, woman, or child with whom he came in contact and especially each who appealed to him for help To all he was sympathetic, courteous, and gentle, with a kindly sense of humour
>
> His restless body with its quick movements seemed the natural partner for his mind—a mind ever hungry for new facts and new thoughts and ever probing for gaps in his own knowledge in order that he might try to fill them In this endeavour he was tireless, talking on the telephone or writing, if that were more convenient, to any expert who might help him to see more clearly the problem of his patient and how he might help There seemed to be no half measure for him when engaged on a problem, but he knew his physical limits and in later years while still busily engaged professionally, he would lie down for a few hours to gain strength for the next task This output of energy, which seemed beyond that of other men, was given not only to his professional work but also to his trout and his salmon fishing, to shooting, to his appreciation of craftsmanship and art, to hospitality, and above all to his friendships Nothing but the best was good enough for him, and he would arrange as efficiently for a day in the country as for a journey to Australia, for a dinner-party in his home as for a critical operation on a person of international importance Worldly success came to him but he only welcomed it in order that he might more readily help others
>
> His example had an educative value impossible to measure, for while his skill in the execution of delicate operations gave him eminence as a surgeon, his study of his patients as persons, of their apprehensions, their worries, and their joys, and his understanding of their disturbed physiological functions were characteristic of the best physicians His daily life was a lesson on how each can make the most of his talents in the service of mankind, and on how to see and seek the best in others

JOHN JOYCE KEEVIL

D S O, M.A, M.D Cantab, D T M. & H, F S.A.,
F.R.Hist.Soc., J.P

Commander Keevil, who died on Dec 16 at the age of 56, had found time in a comparatively short life to win distinction as a naval medical officer and as a medical historian In these last years he had drawn these two careers together, and the first two volumes of his medical history of the navy, the second only lately completed, will be a fitting memorial to a sailor and a scholar

He was educated at Marlborough, Gonville and Caius College, Cambridge, and St Thomas's Hospital Soon after qualifying in 1925 he joined the Malayan Medical Service, but in 1927 he joined the Royal Navy as a surgeon, where he rose to the rank of surgeon commander in 1937

At the beginning of the late war he was senior medical officer of H M S *Illustrious*, the aircraft carrier In January, 1941, the *Illustrious*, while helping to convoy troopships from Gibraltar to Greece, was attacked by a mixed Italian and German force of dive-bombers, high-level bombers, and torpedo-bombers She was hit by 7000 lb of bombs, and 125 officers and men were killed and a greater number injured During the battle, amid blast, flame, and death, Keevil and his two junior medical officers rescued the wounded, rendered first-aid, and performed operations in a dark and flooded theatre

Keevil's critical report on the medical aspect of the battle and his recommendations did much to help the Medical Department of the Admiralty in evolving the new medical organisation for action in H M Ships afloat. In particular, the site and construction of sickbays were reviewed For his services Keevil received the D S O

After a period of service on shore he was appointed the first naval editor of the *Official Medical History of the Second World War* Here his judgment and experience were employed in planning the scope of the naval volumes of the *History* and in collecting material for them Where possible, the framework which Keevil constructed has been followed in the two published volumes A S M writes

Keevil proved a delightful colleague on the editorial committee of the *Medical History* He could be outspoken and critical in his opinions, at times even cynical, but he gave excellent counsel and untiring assistance, and his comments were often spiced with wit He was of medium height, dark, and clean shaven His manner, while always courteous, was somewhat reserved, but this only masked a kind and generous disposition Though always ready to give of his wisdom to other students of medical history, he was modest and unassuming about his own attainments

Keevil resigned the naval editorship to serve at sea again in the concluding years of the war, and retired from the Navy in 1946

For the rest of his life Keevil was a medical historian While serving at sea he had kept up his scholarship, and in 1948 he was appointed the first post-war keeper of the library of the Royal College of Physicians

There he was faced with the literally burdensome task of handling and arranging thousands of books which had been in storage His rearrangement of the library, under the direction of the Harveian librarian, was admirable and he did much research into the *Annals* and manuscripts of the college This work was embodied in his readable biographies of the two Hameys—*Hamey The Stranger* (1952) and *The Stranger's Son* (1953)

His attainments were recognised by election to the Society of Antiquaries, and after he retired from the college he found congenial work as an inspector and adviser on private collections of manuscripts under the National Register of Archives But his chief task and interest was of course his history of the naval medical service, and many will share his colleague W R L 's regret that Keevil "has left his tale half told" Of this important project F H K G relates

When I became scientific secretary of the Wellcome Trust in 1955, the trustees, on Prof T R Elliott's recommendation, had already agreed to sponsor the preparation and publication of this work, and in my second year with the Trust I received from Keevil the typescript of volume I, covering the period 1200 to 1649 It was accompanied by a charming and modest letter in which he said that he would welcome any comments which I, as an experienced editor, would care to make upon it I saw at once that it was a work of rare scholarship, and I soon found that the only suggestions I could make about it related to *trivia* and to points about which a reader less well-informed than the author might be glad of further explanation All these suggestions were received by him with tolerance and gratitude (though many of the queries admittedly were born of my own ignorance), and we became firm friends

At the time when volume I was published last summer, Keevil had already had the first severe attack of his illness As soon as he was allowed to resume work he completed the writing of volume II, but in continuing the history he was handicapped by no longer being able to come up to London to work in the libraries, particularly that of the Royal Hospital at Greenwich, on which he depended so largely for source material for volume III I was therefore glad that I was able to introduce to him Dr Edwin Clarke, who could help him with the library research Thanks to the author's indomitable spirit, and the support and help of his wife—herself a writer of distinction—the typescript of volume II was sent to press a few weeks ago, and on the day that Keevil died I received from him an optimistic letter indicating that volume III was beginning to take shape That volume and the intended final volume must, it seems, be lost to us, but it is good to know that Keevil had the satisfaction of seeing uniformly enthusiastic press notices of his first volume, and that volume II, bringing the story of British naval medicine to the year 1714, will in due course appear as a further important contribution to British historical scholarship, and a lasting memorial to a remarkable man

Commander Keevil married in 1946 Averil Salmon, daughter of Robert Mackenzie-Grieve of Torrington, and she survives him

THOMAS RICHARD GODDARD

M R C S

Dr Goddard, who died on Dec 17, qualified from University College Hospital in 1925, and soon afterwards settled in practice at Hemel Hempstead He remained there until he retired a few years ago to Berkhamsted Of Dr Goddard's eventful and unorthodox apprenticeship to medicine his old chief P H M -B writes

When I was ordered up from Cairo in 1917 to organise a field laboratory in close contact with the large casualty-clearing station at Rafa behind the Gaza front, I found Sergeant Tom Goddard there as my main prop, and it was largely due to his knowledge of laboratory technique, skill, and efficiency that this vital laboratory service was in working order within 4 hours From that time onwards until we were demobilised in 1919, we worked together There was no lack of material, for we were really part and parcel of the adjoining hospital so that we were immersed in the diagnosis of dysentery, malaria, relapsing fever, typhoid, and many other disorders all day long and often far into the night Not infrequently we handled 50 specimens of faeces a day and sometimes even more

It was Goddard who helped to organise the malaria diagnosis stations without which Allenby might not have advanced to Aleppo in September, 1918, and on him I relied to help train our personnel in the intricacies of hæmatology and malaria diagnosis for this task. It was he who concocted the MacConkey's media upon which he cultivated the dysentery bacilli in those memorable days, and it was he who helped to isolate cholera vibrios on Dieudonné's medium, when an epidemic threatened the Army at a critical time early in 1918 and which was scotched by the detection and elimination of carriers "inside three weeks"

Goddard, too, was always interested in our private zoo, where we had cages containing desert rats, gerbils, and jerboas which wandered into our tent at night, and little owls, quail, corncrakes, larks, and various warblers which flew in in the daytime Sometimes he was called upon to deal with camel convoys which arrived at the modest E P I P tent, which served as our main laboratory, laden with stools from suspects as far away as Beersheba

In the rough-and-tumble of war pathology Goddard could always be relied on to be loyal, competent, and efficient, and the experience he gained served him in good stead when he decided to take up medicine directly after demobilisation So keen and studious was he that he soon completed his medical course and settled down as a most capable and successful family doctor

ARTHUR JAMES EWINS

D Sc Lond , F R S

Dr A J Ewins, director of research to May & Baker Ltd , who died on Dec 24 at the age of 75, was associated with the late Sir Lionel Whitby in the joint investigation which led to the introduction of sulphapyridine Though this drug has now been largely superseded by newer remedies, its workaday laboratory name (M & B 693) caught the public imagination and "M & B" is still widely, if inaccurately, used for any sulpha derivative

Ewins was the son of a railwayman in South London He won a scholarship to Alleyn's School, Dulwich, and later worked as a technician at the Wellcome Laboratories, then at Herne Hill With the help of evening classes he took his B SC Lond in 1906 and joined the scientific staff of the laboratory In 1914 he took the D SC , and the same year he moved, with his chief Sir Henry Dale, to the Medical Research Committee which had been set up the outbreak of war Part of Ewins' work was to range for the production of German drugs by British ms, and this association led in due course to his pointment as head of the chemical research department May & Baker He was responsible for the firm's search programme which in the '30s led to the development not only of sulphonamides but also of diamidine mpounds which have proved efficacious in tropical edicine Dr Ewins was elected F R S in 1943

A memorial service for Dr Maurice Mitman will be held at yce Green Hospital, Dartford, on Monday, Jan 13, at 3 P M ckets for the service can be had from the secretary, the Bow Arrow ospital, Dartford

Diary of the Week

JAN 5 TO 11

uesday, 7th

NIVERSITY OF LONDON
5.30 P M (London Hospital Medical College, E 1) Dr E Jacobsen (Copenhagen) Pharmacological Classification of Central Nervous Depressants
NSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5.30 P M Mr B E D Cooke Disorders of Buccal Mucosa

Wednesday, 8th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M. Dr John Loutit Successful Transplantation of Homologous and Heterologous Tissue in the Experimental Mouse
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P.M. Dr Howard Nicholson Chronic Pulmonary Suppuration
INSTITUTE OF DERMATOLOGY
5.30 P M Dr Arthur Tickner Biochemistry of Hormones—Steroids
NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY, 64, St. James' Street, Nottingham
8 30 P M Dr Roger Ormrod Negligence
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P.M. (Royal College of Surgeons 18, Nicolson Street, Edinburgh.) Dr J G M Hamilton, Prof J H Gaddum, Prof John Bruce Medicine in Russia

Thursday, 9th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr Matthew Thomson Some Aspects of Industrial Dermatitis (Watson Smith lecture)
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P M Lord Evans Significant Hypertension

Friday, 10th

POSTGRADUATE MEDICAL SCHOOL
10 A.M Mr J C. Barrett Multiple Primary Malignant Neoplasms
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C.1
3.30 P.M. Mr Anthony Radcliffe Hoarseness

Appointments

CZYNIEWSKI J P, M D Lwow, D A anæsthetist (S.H.M O), East Cumberland group of hospitals
HAMSHAW, DORA, B.SC. Lond., M.R C.S, D C.H. assistant M O, York.
HARRISON, KENNETH, M.D Manc., F.R.C.S, D.L.O part-time consultant E N T surgeon Stockport and Buxton group of hospitals
JONES BRENDA, M.B Lpool D.P.H assistant M.O.H and school M O, Southport
SIMPSON J H, M.D Cantab, M R.C.P consultant physician with an interest in geriatrics, Exeter clinical area

Newcastle Regional Hospital Board
- HARRIS, HILDA R., M.B. Manc., M R.C.P.E., D.PATH assistant pathologist (S.H.M O) Hartlepools group of hospitals
- MCCLEMONT, JOHN, M.B Edin, D O.M.S consultant ophthalmologist, Darlington, Northallerton, and South West Durham groups of hospitals.
- MITCHELL, J C., M.D Aberd consultant pathologist, Newcastle upon Tyne group of hospitals

County Borough of West Hartlepool
- BISSET, JANET M, M.B. Edin., D C.H assistant M.O.H (maternity and child welfare)
- MILLIGAN H C., M.B. Edin, D P.H M.O.H.
- TERRY, S W W, M.B Madras D T.M & H, D.P.H deputy M.O.H.

Births, Marriages, and Deaths

BIRTHS

KAY—On Dec. 23 at the Cardiff Maternity Hospital to Beverley (nee Bryce) wife of Dr Michael Doveton Kay a son—Michael Graham Doveton

DEATHS

HALL—On Dec. 26 1957, at 16 Pilgrims Lane London N W.3 Edith May Hall M.D, F R C.S., F.R.C.O G

Notes and News

CLEAN AIR

IN 1306 a citizen was tried and executed in London for burning "sea cole", and though few of our modern reformers would favour so vigorous a remedy, the damage done by smoke to our health and economy has aroused the zeal and outcries of reformers since John Evelyn's *Fumifugium* of 1661, and even earlier The Coal Smoke Abatement Society was founded in London in 1899, and in 1929 it fused with the provincial Smoke Abatement League of Great Britain to form The National Smoke Abatement Society These societies have led the clean-air movement throughout the century, in the face of apathy, lack of financial support (for smoke abatement is not so romantic a cause as some less worthy), and even derision They began the study of air pollution that is now made under Government auspices, they pioneered training-schemes for boiler-operators, and they conceived the idea of smokeless zones Many of their views and policies were endorsed by the Beaver Committee, whose report led to the Clean Air Act

On Jan 1, the society changed its name to the National Society for Clean Air, in recognition of its widening scope, and became an incorporated body, it is a company limited by guarantee, without share capital, and with permission to omit the word "limited" from its title

The Beaver Committee estimated that the most heavily polluted areas could be made smokeless in ten to fifteen years if smoke-control areas totalling 300,000 acres could be established yearly, but the total for 1957 was 489, and the total projected for 1958 less than 10,000 acres Giving these figures, the society call attention to the need for continued and increasing instruction and publicity directed at authority and at the public, they encourage new members and donations to help in their important work, which includes the encouragement of research and of the application of new developments

GERIATRIC UNIT AT DUNDEE

At a cost of £45,000, the geriatric unit at Maryfield Hospital, Dundee, has been reconstructed It has been receiving patients since August, and it was visited by Princess Margaret on Dec 6

Accommodating 29 men and 30 women, on separate floors, it has for each sex four small wards and two sittingrooms Confused and incontinent patients can be segregated from the mentally alert, and patients are promoted to the better wards as soon as their condition improves sufficiently

The unit is complete in itself, with facilities for radiography, physiotherapy, and occupational therapy Full use can be made in addition of the specialist services of the general hospital. The local health authority has plans well advanced for the provision of halfway-house accommodation both by the reconstruction of existing buildings and by new building

The consultant physician in charge of the unit is Dr O Taylor Brown. The staff consists of a registrar, Dr A B Grant, and two house-officers The nursing staff, beside the two ward sisters, consists of staff nurses, student nurses, and nursing auxiliaries, with a proportion of male staff in the male ward. Dr Taylor Brown is lecturer in geriatrics to the University of St. Andrews and regular ward teaching takes place in the unit.

The Medical Society for the Care of the Elderly holds its spring meeting in Dundee on March 28 and 29, when a visit to this attractive unit will be part of the programme

HOSPITAL WORK ON TELEVISION

A series of programmes from regional hospitals is to be televised by the B B C from Feb 11 The first, dealing with poliomyelitis, will come from the Churchill Hospital [illegible] and the second, on cancer, from the Christie Hospital and Holt Radium Institute in Manchester The surgery of the circulation will be illustrated in three programmes—a [illegible] valvotomy at Queen Elizabeth Hospital, Birmingham, a [illegible] caval shunt from Bristol Royal Infirmary, and a third operation to be shown at Leeds Infirmary. The work of a cottage [illegible] will be displayed at Stratton Hospital, Cornwall, and a programme on psychiatry from the Southern General Hospital, Glasgow, will include a filmed sequence showing Crichton Royal Mental Hospital, Dumfries Wales will be represented by a programme on tuberculosis from Sully Hospital, Cardiff, and on pneumoconiosis from Llandough, Penarth A brain operation is to be shown at the Royal Infirmary, Edinburgh

The B B C hopes that members of the medical profession will see these programmes and would be pleased to have comments on them from doctors

CHRISTMAS QUIZ

Dr J B Gurney Smith points out that the " original set of posers " provided by Dr Ffrangcon Roberts in our issue of Dec 21 assign Dr Robert Bridges to the wrong hospital He trained at St Bartholomew's, not St Thomas's, and some of his early verses appeared in *Round the Fountain*

University of Cambridge

On Dec 14 the degree of M D was conferred on the following

P S Andrews, Edward Sharp, H H Stewart, S E Trickey

University of London

Dr E G L Bywaters, senior lecturer at the Postgraduate Medical School of London, has been appointed to the new Empire Rheumatism Council chair of rheumatology at the school We announced the endowment of the chair last week

Dr Bywaters, who graduated M B Lond with honours from the Middlesex Hospital in 1933, was appointed in the following year to a Mackenzie-Mackinnon research scholarship of the Royal College to study rheumatoid arthritis After visiting the United States with a Rockefeller fellowship he became clinical pathologist at the Bland-Sutton Institute of the Middlesex Hospital and later deputy director of the M R C unit at the Royal Victoria Infirmary, Newcastle-upon-Tyne, and besides his lectureship at the school he also holds at present the directorship of the research unit at the Canadian Red Cross Memorial Hospital at Taplow His published work includes papers on the metabolism of the joint spaces and during the late war he was one of the team which investigated the effect of crush injuries on renal function

University of Leeds

At recent examinations the following were successful

M D—R E Rossall
Ch M—M G Wilson
Ph D—J A Sharp
M B , Ch B—Geoffrey Hoyle (with second-class honours), T L Avery, Pamela M W Barker, J E Berry, Ian Bower, Barrie Breeze-Stringfellow, J M Brook, Charlotte N Capes, R B Dobson F E Eteng, Paul Foggitt, L F Gendall, T M Hall, Joyce M Handby, D A W Hopkinson, J L Horner, D A House, H A Hunt, R C Ingrey-Senn, P J Knapton, Margaret E Lane D R Liddle, M D McGrath, J C Nicholson, John Norman, Aleksandra M Schwetz, Neville Seymour, J M Sinclair, P Yuk Fen Taikie, Eifion Treharne, Marion E Tyler, Sarah A Williams

University of Bristol

At recent examinations the following were successful

M B , Ch B—M G Addy, A A Codd, J C G Cole, J S Edmondson, R R Gibbins, D H Howton, Osafo Lartey, J G Meadows, K J Roper, G A Russell, R F Weeks, R C Williams

University of Liverpool

At a special congregation on May 7 to mark the opening of the new medical school by Queen Elizabeth the Queen Mother the honorary degree of LL D will be conferred on Lord Adrian, Sir David Campbell, and Sir Allen Daley

University of Edinburgh

Mr J I P James has been appointed to the George Harrison Law chair of orthopædic surgery in succession to Sir Walter Mercer He is expected to take up his appointment in the spring

Mr James who is 44 qualified from University College Hospital, London, in 1934 and two years later took the F R.C.S In 1941 he became part-time registrar in the Royal National Orthopædic Hospital London, and a year later surgical registrar at U C H The same year he obtained the M S Lond In 1943 he joined the R.A M C and served with a special airborne force as a forward surgeon with guerilla forces in Yugoslavia and as orthopædic surgeon to the forces in Greece When he was demobilised he held the rank of lieut.-colonel and was officer commanding the surgical division of a general hospital Since 1946 he has been orthopædic surgeon at the Royal National Orthopædic Hospital and he is also assistant director of studies at the Institute of Orthopædics, London University and civilian consultant orthopædic surgeon to the Royal Navy In 1947-48 with a Rockefeller fellowship he worked in orthopædic centres at Boston, New York, and San Francisco In 1956 he gave a Hunterian lecture on paralytic scoliosis and his other published work includes papers on the treatment of curvature of the spine and on reconstructive surgery of the hand

Airborne Medical Society

A meeting of this society will be held on Friday, Jan. 31, at 5 30 p m at St Mary's Hospital, London, W 2

Institute of Dermatology, London

A semi permanent exhibition on the normal epidermis and some precancerous conditions by Dr H Haber, will be held from Jan 1 to 17 at the institute, Lisle Street, W C 2

The Prime Minister and the Whitley Award

On Dec 23 Mr Harold Macmillan received a deputation led by Mr Ben Smith, chairman of the staff side of the General Council of Whitley Councils, and explained that under present economic conditions it was not possible to lift the Ministerial veto on a 3% increase for administrative and clerical staff in the National Health Service

British Journal of Tuberculosis

The editor of this journal, Dr Philip Ellman, is to have an assistant editor, and Mr J R Belcher has been appointed Prof Charles Cameron, Dr Maurice Davidson, and Dr Reginald Ellis are retiring from the editorial board and Dr Frank Scadding, Dr I W Grant, and Dr R Y Keers have been appointed in their place Prof O L Wade is to be an additional representative on the board

Spastics in the West of Scotland

A year ago a new residential school, Scotscraig, was opened in Paisley under the direction of the Scottish Council for the Care of Spastics The Council's first school, Westerlea, was started in Edinburgh in 1947 When extensions planned for the Paisley school have been completed, it should have enough places to educate and treat suitable children from the West of Scotland

At present it has 8 resident pupils and 4 day pupils, 17 other children who go to school elsewhere or are below school age, attend for physiotherapy or speech therapy Future plans include an extension of outpatient treatment by a team of therapists visiting outlying centres and a nursery school for preschool children Children are selected by a screening panel consisting of an orthopædic surgeon, a pædiatrician, a child psychiatrist, and an educational psychologist Arrangements for screening are made with the social worker, Scotscraig, Park Road, Paisley

Medical Research Council

The Council invite applications for the following fellowships for 1958–59

Fellowships in Clinical Research—The Council are offering a further series of fellowships in clinical research, tenable at centres in the United Kingdom These fellowships are open to suitably qualified medical graduates who wish to prepare for a career in clinical research

Rockefeller Travelling Fellowships—These fellowships are intended for graduates resident in this country who have had some training in research work in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad before taking up appointments for higher teaching or research in the United Kingdom

Dorothy Temple Cross Fellowships in Tuberculosis—These fellowships offer special opportunities for study or research to British doctors who intend to devote themselves to the advancement by teaching or research of curative or preventive treatment of tuberculosis ' The fellowships will, as a rule be awarded to candidates who wish to make their studies or inquiries elsewhere than in the United Kingdom

Alexander Pigott Wernher Fellowships in Ophthalmology and Otology—These fellowships are intended for doctors who are likely to profit by a period of work in ophthalmology or otology at a centre abroad before taking up positions for higher teaching and research in these branches of medical science The awards will normally be tenable for one year

United States Public Health Service Research Fellowships—A limited number of these fellowships are being offered to highly qualified scientists from outside the United States to work in the medical and biological laboratories of the United States British doctors should apply in the first instance to the Medical Research Council

French Government Exchange Scholarships—Under the terms of a reciprocal arrangement with the Centre National de la Recherche Scientifique two scholarships tenable at research institutions in France are offered to British workers in medical science The scholarships will normally carry a maintenance allowance of 50,000–70,000 francs a month

All the fellowships provide for the payment of a maintenance allowance at the rate of £650 per annum for a single fellow or £900 per annum for a married fellow ($3000 and $4200 respectively if the fellowship is held in the United States) Allowances are made for travelling and other approved expenses Forms of application for these fellowships may be had from the secretary of the Council, 38, Old Queen Street, London, S W 1, with whom applications must be lodged by March 1 (March 31 for the Pigott Wernher fellowships and the French scholarships)

Mr A L d Abreu is visiting Peru from Jan 5 to Feb 6 under the sponsorship of the British Council He will give twelve lectures on thoracic surgery at the tuberculosis hospital at Lima

The Lancet · Saturday 11 January 1958

REGULATION OF BODY TEMPERATURE IN HEALTH AND DISEASE*

SIR GEORGE PICKERING
M.A., M.D. Cantab., F.R.C.P., Hon. F.A.C.P.
REGIUS PROFESSOR OF MEDICINE IN THE UNIVERSITY OF OXFORD

(concluded from p. 9)

MY first lecture was concerned with the mechanisms with which a healthy man regulates his body temperature. Now I wish to consider briefly the very low and very high temperatures which may be produced by breaking through this regulating mechanism, and to consider more fully the problem of fever which results from a disturbance in the regulating mechanism.

Hypothermia

It has been known for a long time (Boyle 1683) that fish may be imprisoned in ice, and may even become partly frozen, and yet recover when the temperature is raised. With the approach of winter some mammals (e.g., the marmot and the dormouse) retire to their burrows, curl up, and become drowsy, their body temperature falls to a little above that of their surroundings, and their heart-rates, respiration-rates, and metabolic rates fall to low levels. From warm-blooded they have changed to cold-blooded animals. The capacity to do this is widely distributed in mammals, being found in rodents (beavers), insectivores (hedgehogs), and carnivores (bears). It is rare in birds, but the "Poor Will" of the Western United States is said truly to hibernate (Fisher 1953).

Dr. Audrey Smith (1956) has shown that the hamster can be cooled to temperatures below freezing-point. When the temperature of the parietes falls to about −5°C, ice crystals form, the process of supercooling is arrested, and the temperature rises. As a consequence of the freezing of water, the electrolyte concentration of the remaining fluid rises, and, when it has doubled in the extracellular fluid, the cells are irreversibly damaged (Lovelock and Smith 1956). Even though superficial parts of the hamster form a shell of ice crystals, the animal may recover if it is gently warmed—e.g., by immersion in warm water—particularly if it has frozen progressively for not longer than 50 minutes, but less often if it has crystallised after supercooling below −3.5°C. The frozen animal has, of course, no heart-beat and no respiration, and artificial respiration is required during warming.

Rats do not hibernate. Andjus (1951), however, showed that a small proportion of these animals cooled to between 0 and +2°C could also be reanimated after heart and breathing had stopped for 40–50 minutes, and improvement of technique brought about the survival of 75–100% of animals so cooled (Andjus and Smith 1955). The learning of rats so cooled and reanimated was definitely impaired when cooling had proceeded to between +1 and 0°C, but no impairment was demonstrated when the lowest temperature reached was between +13.4 and +18.5°C (Andjus et al. 1956).

The theoretical and practical importance of these observations needs no emphasis. Here in fact is a breaking through of the barrier between Bernard's "*la vie constante*" to "*la vie oscillante*" and even to "*la vie non-manifestee*". Moreover it is becoming increasingly evident that, at low temperatures, operations, particularly those involving heart, large blood-vessels, and brain, are possible that would have had disastrous results at normal temperature. A large literature has grown up on hypothermia or artificial hibernation in man, and I shall not attempt to review it here. I shall only make four points.

(1) The practical difficulty in cooling men is to break through the defences of the body; the most effective means is to give an anæsthetic, which (as we have seen) has been shown to interrupt at some point or points the reflex arcs which protect against cooling, particularly by shivering.

(2) Consciousness generally seems to be clouded or lost at rectal temperatures between 29 and 31°C.

(3) At temperatures below 30°C glucose is metabolised slowly or not at all (Wynn 1954).

(4) Finally and most important, the lethal temperature seems to be between 25 and 27°C, when ventricular fibrillation occurs. The exact mechanism by which ventricular fibrillation is precipitated in cold men is thus the outstanding practical problem, if the full possibilities of this line of treatment are to be developed.

Hyperthermia

It has also long been known that, in very hot weather, particularly after exposure to strong sun, men may become comatose and die. Medicine, in its omniscience, was of course at hand with an explanation, and this illness was attributed to the actinic rays of the sun striking through the back of the neck to the vital centres in the medulla. Hence the pith helmet and those cloths that draped the back of the helmet in India a century ago. It is known now that this illness is heatstroke, a breakdown of the regulating devices of the body with the result that the temperature rises usually above 106°F. I know of three good accounts, that of Lambert (1897) describing an epidemic in New York, that of Ferris et al. (1938) describing an outbreak in Cincinnati, and that of Ladell, Waterlow, and Hudson (1944) describing their experiences with British and Commonwealth troops in the Middle East.

Of the Cincinnati patients only seven were under 50 years old, and most were exposed to the highest temperatures—e.g., living in a top flat under a flat roof which got much heated by the sun. Absence of sweating was noted in all, most were in coma and incontinent of fæces. When they were treated with ice-water applied to the skin, there was a rapid fall of temperature, consciousness being regained about 106–107°C, when goose-skin was also frequently noted. The sodium-chloride level in the blood was normal. The cessation of sweating was noted to be a common precipitating factor in these cases, as it was in those of Ladell et al. (1944).

Lambert (1897) found in the New York epidemic that every patient with a temperature of 110°F or over was completely comatose. Of seventy-three patients admitted to hospital and subsequently traced, three were found to be insane.

These observations may be compared with those on therapeutic hyperthermia, at one time used to treat syphilis and gonorrhœa, described by many workers—e.g., Wallace and Bushby (1944). The aim of such treatment was to achieve a temperature of 106°F for 8 hours. Most of the patients became disorientated, and many showed herpes labialis on recovery. These are two of the striking features of lobar pneumonia, often attributed to that (to me mysterious) state "toxæmia" but apparently attributable simply to the effect of temperature. Arterial anoxia and bilirubinæmia were common. Lambert noted anæmia as a common sequel of sunstroke in the New York epidemic.

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* The Croonian lectures for 1957, delivered on May 14 and May 16 before the Royal College of Physicians of London.

Fever

By far the most important of the disturbances of body temperature is fever, which may be defined as a raised central temperature consequent on a disturbance of the thermotaxic mechanism

One cause of fever may be disposed of at once—namely, a lesion of the central nervous system, particularly of the basal ganglia These lesions presumably destroy part of the central receptors or their connections In view of the results of experiments on animals it is rather surprising that such lesions have never been observed to produce falls but only rises in body temperature These rises are often extreme Thus of Bryant's hundred cases of hyperpyrexia (over 106°F) twenty-two were due to brain lesions, and all those patients died Little more can be learnt from such cases The commonest lesion is cerebral hæmorrhage, which usually causes extensive disruption of the brain, the basal ganglia are generally involved, and rupture into the ventricles is common

Causes

In the remaining, and much more numerous, instances, fever is the result of a functional disturbance of the thermotaxic mechanism The commonest causes are (1) infections or infestations, and (2) lesions which destroy tissues

Infecting agents include viruses (e g , poliomyelitis), bacteria (e g , pneumonia), protozoa (e g , malaria), and fungi (e g , actinomycosis) Even the nematode worms may be involved, invasion of the tissues by *Trichinella spiralis*, or of the lungs by ascaris, may produce fever, associated in each case with a large increase in the eosinophil cells of the blood In the absence of infections, fever due to lesions causing tissue destruction is usually slight, such lesions are infarction (e g , of the heart), malignant tumours (particularly when the growth is extensive or metastasising in liver), and gout

Because of these two types of lesion causing it, the mechanism of fever has been sought in the chemical constituents of invading microorganisms, on the one hand, and of the body cells of the host on the other Here we may note that fever has other causes whose nature is obscure Thus rheumatic fever is currently conceived to represent an immune reaction between the antigens of a particular strain of streptococcus (Lancefield group A, B hæmolytic) and the antibodies of the host Half a century ago this disease was a common cause of hyperpyrexia, comprising 6% of Bryant's cases, and being the commonest cause in the wards of Guy's Hospital after nervous lesions and pyæmia Another curious instance is hæmorrhage, a rise of temperature up to 100 or 101°F is common after gastrointestinal bleeding

Of these instances of naturally occurring fever, by far the most carefully investigated is malaria

Characteristically, paroxysms of fever occur on the third day (every 48 hours) in benign and malignant tertian malaria (*Plasmodium vivax* and *falciparum*) or on the fourth day in the quartan form (*P malariæ*) These intervals correspond to the times taken for the merozoites to invade the red cells, subdivide within them, and finally break through the red-cell envelope into the bloodstream The onset of fever is thought to correspond approximately to the rupture of the red cells and the entry of the merozoites into the bloodstream

Virchow (1854) conceived of fever as a weakness—a failure to control heart, blood-vessels, and metabolism through the moderating centre Traube (1864) discovered that in fever the elimination of nitrogen is increased He supposed that this was secondary to a circulatory disturbance, that a fever-producing agent produced, through the tonic vasomotor nerves, contraction of the peripheral arterioles, with a consequent decline in surface temperature and rise in deep temperature Von Liebermeister (1875) developed Traube's hypothesis and concluded from his experiments that, in fever as in health constancy of body temperature is ensured by the adaptation of heat production to discharge, and that in fever the body temperature is regulated in the same way as in health, except that the norm is higher In general Von Liebermeister's concept of the nature of the disturbance that constitutes fever is widely accepted still As we shall see, it explains many of the facts, but new data have become available that lie entirely outside his hypothesis With this introduction we may look more closely at the established facts

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It is customary to divide a fever into three phases (1) the phase of rising temperature, the chill or ague, (2) the phase of steady pyrexia, the fastigium or flush, and (3) the phase of falling temperature, the sweating phase or defervescence The first and last phases are most easily studied in brief bouts of fever whose onset and duration are predictable Such are malaria and the fever produced by injection of pyrogens

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The *fastigium* is most easily studied in pneumonia or in typhoid where the temperature remains high for several successive days It shows the same diurnal variations as in health, the peak being reached in the early evening and the trough in the early morning, but the fluctuations are usually larger It is from this phase comes the chief evidence for Von Liebermeister's hypothesis

Stern (1892) found that, when the body was immersed in a hot bath, sweating began after the same rise of temperature (0 1–0 8°C) in febrile as in normal people, conversely, immersion in a cool bath produced shivering after similar falls Schwenkenbecher and Tuteur (1907) observed that food produced similar increases in water loss from the skin in normal people and in patients with typhoid In continuous fever they observed that the water loss from the skin is increased Cecil, Barr, and DuBois (1922) observed that in continuous fever both heat production and heat elimination are increased, the increase in heat production above the normal averaging about 13% of basal per 1°C rise in body temperature

The *defervescence* or phase of fall of temperature is seen at its most striking in the crisis of pneumonia and in the sweating stage of the malarial attack The patient feels very hot, he flings off his bedclothes and begins to sweat profusely. Clearly the fall of temperature is due to the mobilisation of all the mechanisms that increase heat loss.

In general, these phenomena can be interpreted in terms of Von Liebermeister's hypothesis. If we assume that, in the first phase, the setting of the thermotaxic mechanism is raised, we should expect the events during this phase to resemble those produced by exposing a healthy person to cold. Again during the fastigium temperature is regulated at a new and high level, and the usual defences are mobilised against a deviation up or down. Finally, the defervescence would be ascribed to a reduction in the level at which the mechanism is set, the response of the body should mimic that produced by exposure to heat, as it does. Nevertheless the methods used to test the hypothesis in the past have been relatively crude, and it is to be hoped that an opportunity will be found to see whether the central and peripheral receptors behave quantitatively in fever as Snell and Cooper have found them to behave in health.

Most of the phenomena of fever can be explained on this hypothesis or the effect of the raised temperature itself. Thus a rise in heart-rate and respiratory rate is produced by heating the body—though the relatively slow pulse in typhoid and high respiratory rate in pneumonia are exceptions. Again, the increased metabolic rate, together with anorexia, may largely explain the increased excretion of nitrogen and the tendency to muscular wasting, though, as Wright (1950) has emphasised, the major defence reactions of the body also involve large syntheses of protein. However, one set of vascular responses is now known that cannot be so explained, and to that we may now devote our attention.

Responses Unrelated to Thermotaxis

These responses were discovered accidentally by Homer Smith and his colleagues during investigations on the behaviour of the kidney: a sample of inulin, which they were using to estimate the glomerular filtration-rate, proved to be pyrogenic, and they were surprised to find that it produced a pronounced increase in the apparent renal blood-flow. Further and detailed investigation showed that the initial phase of the febrile response, the chill, is accompanied by a rise of blood-pressure and a decrease in glomerular filtration-rate and in renal plasma-flow. The phase of sustained pyrexia is accompanied by a fall of arterial pressure and a slight rise in glomerular filtration-rate and a much larger increase in renal blood-flow (Goldring et al. 1941). The fall of arterial pressure is much greater in persons with high blood-pressure, as indeed is true with most responses (Pickering 1955). Now, the fall in arterial pressure and the renal vasodilatation are not due to the rise in body-temperature, nor are they an essential component in producing it, for they both occur after the injection of a bacterial pyrogen, even though the fever is prevented with amidopyrine. These vascular responses thus seem to represent another effect of bacterial pyrogens, distinct from their effect on the thermotaxic mechanism.

Pyrogens

It is now apposite to turn our attention to the problem of pyrogens—i.e., substances which produce fever on parenteral injection. These substances have been sought in many places and found in two—namely, in bacteria, and in polymorphonuclear leucocytes.

The history of the investigation of bacterial pyrogens is fully reviewed by Bennett and Beeson (1950). Intravenous injection of the dead bodies of most gram-negative bacteria produces fever. Contamination with bacterial debris is now recognised as the cause of water fever, of salt fever, and of sugar fever (i.e., of pyrexia following intravenous injection of these fluids), and, as Hort and Penfold (1912) showed, the contaminating agents are of such a size that they pass a filter candle but not the gelatin filter devised by Martin. Lüderitz and Westphal (1952) have identified the pyrogen of *Escherichia coli* as a lipopolysaccharide of high molecular weight and containing 74% of phosphorylated polysaccharide and 26% of lipoid. The sugars obtained by hydrolysis of the polysaccharide include rhamnose, xylose, glucose, galactose, and *N*-acetyl hexosamine. 0·1 μg of this substance injected intravenously is enough to produce fever in man. Like other bacterial pyrogens, this substance is not dialysable, it is not destroyed by boiling or autoclaving but is destroyed by dry heat at 160°C.

Oddly enough, no pyrogens have yet been found in gram-positive cocci. Thus, the bodies of dead pneumococci injected intravenously produce no fever (Bennett 1956c), despite the fact that the fever accompanying pneumococcal infection is one of the most intense encountered in man.

Because, as we have seen, mild or moderate fever is a common accompaniment of tissue destruction in man, several workers have sought pyrogens in tissue extracts. One of the first to report success was Menkin (1945), who showed that extracts of pus were pyrogenic, and named the active substance "pyrexin". However, the sample which Bennett and Beeson (1953b) investigated behaved more like a bacterial pyrogen, and the exact status of pyrexin remains uncertain.

The most thorough of such investigations is that of Bennett and Beeson (1953a), who, taking great care to avoid bacterial contamination, made saline extracts of various tissues in the rabbit, and found only one tissue that produced fever—namely the polymorphonuclear leucocytes. These they obtained from the buffy coat of the blood and from the peritoneal exudate induced by injecting physiological saline solution four hours previously. The pyrogenic agent found in leucocytes is quite different from that found in bacteria. Like that, it is not dialysable, but it is destroyed by boiling, but not by trypsin, chymotrypsin, or ribonuclease (Bennett and Beeson 1953b).

Again, oddly enough, no pyrogen has yet been obtained from human leucocytes. Cranston, Goodale, and Wendt, working in my laboratory, have not yet been able to produce fever with extracts of human leucocytes made by shaking them with glass beads, by freezing and thawing them, or by lysing them with water.

Mechanism by which Bacterial Pyrogens Produce Fever

When a bacterial pyrogen is injected intravenously into an animal, fever does not begin at once but only after a latent period of about quarter of an hour in the rabbit and 50 minutes in man. This, together with the fact that fever is known to occur in man in the absence of bacterial infection, led to search for a common factor, such as an intermediate substance produced by the interaction of bacterial pyrogens on the tissues of the body. Menkin's work has been noted. Beeson (1947) observed that, after large doses of bacterial pyrogen, little trace of any pyrogen was found in blood removed 8–10 minutes later, at 4–6

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Armin and Grant (1957) have shown that, after the ntravenous injection of an *Esch coli* vaccine, the denervated ear of the rabbit shows two phases of constriction—one at about 5 minutes, and the other at about an hour, after the injection The first is probably due to the release of a histamine-like substance, and the second to release of substances like adrenaline and 5-hydroxytryptamine It is interesting that the delayed release occurs at a time when the normal ear (which is less sensitive to chemical stimuli) is vasodilated through nervous action

Effect of Pyrogens in Man

The first investigation of the initial process in the action of bacterial pyrogens in man was that of Gerbrandy, Cranston, and Snell (1954) Using both a killed *Esch coli* preparation ('Pyrifer') and a polysaccharide fraction obtained from pseudomonas ('Piromen'), they found that intravenous injection in normal subjects produced a fall of heat elimination from the hand, a rise in mouth temperature, and a rise in rectal temperature, after latent periods of 76 2, 71 1, and 73 5 minutes respectively (fig 6) When the same dose of pyrogen was incubated for $2^1/_2$–$3^1/_2$ hours at 37°C in 17–250 ml of the person's own blood, the latent periods of the responses were 16 5, 19 2, and 25 5 minutes respectively

These are large differences, about 50–60 minutes, and it seems even clearer in man than it was in the rabbit that the initial process in the action of a bacterial pyrogen is with a component of the blood Cranston, Goodale, Snell, and Wendt (1956) have shown that the tissue component is probably the polymorphonuclear leucocyte Unlike that of the rabbit, human plasma or serum incubated with bacterial pyrogen neither accelerates nor augments the fever that ensues after its injection In fact both serum and plasma reduce the febrile response, the effect being destroyed by previously heating serum to 56°C for 30 minutes (Goodale et al 1956) This effect may perhaps be correlated with the evidence of Rowley et al (1956) that normal serum splits bacterial polysaccharide, an effect likewise inhibited by previously heating the serum to 56°C

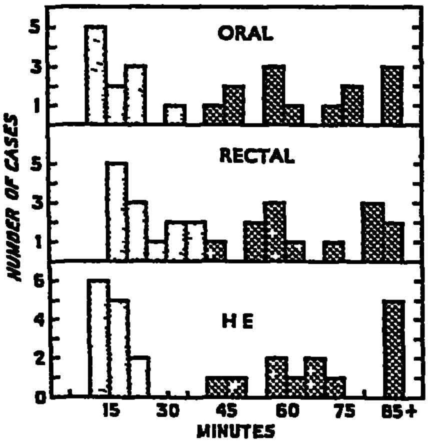

Fig 6—Latent periods between injections of pyrogen and changes in oral and rectal temperature and in elimination of heat from hand (H.E. stippled, pyrogen incubated in fresh blood hatched, control injections of pyrogen Gerbrandy et al (1954)

If, on the other hand, pyrogen is incubated with the cellular fraction of the blood and then injected, the fever is of rapid onset By using fractions containing different proportions of red cells, white cells, and platelets, Cranston et al (1956) show that there is a clear correlation between the incidence of fever of rapid onset and the number of white cells in the preparation, but none with the numbers of red cells or of platelets

If bacterial pyrogen is incubated with a preparation of white cells suspended in saline solution, the rapidly acting pyrogenic substance is found in the supernatant fluid after spinning off the cells Its chemical properties can thus be investigated It has been shown that it does not dialyse, that it is precipitated by saturation with ammonium sulphate, and that it is destroyed by heating to 70°C for 30 minutes The properties of this endogenous pyrogen are thus in a broad way similar to those of the pyrogen obtained by Bennett and Beeson (1953a and b) from the normal leucocytes of the rabbit It is more likely to be derived from the leucocytes (by the action on them of bacterial pyrogen) than to be derived from the bacterial pyrogen itself On the other hand, if this view is correct, incubation with pyrogen should produce some morphological change in the white cells, but no such change has yet been observed, nor are the white cells destroyed Again, one would expect that a similar substance might be liberated when white cells are lysed, but this has not been demonstrated

Discussion

The evidence now seems strong that, sometimes at least, fever in man is due to the release of a substance ("endogenous pyrogen") from leucocytes, through the action of bacterial pyrogens on them. In the rabbit the tissue reactant seems to be found in plasma or serum In the rabbit pyrogenic substance can be extracted from normal leucocytes and seems to have properties similar to those of the endogenous pyrogen released from human white cells by bacterial pyrogen As yet no similar substance has been extracted from normal human white cells

The phenomenon of tolerance suggests that, in man and the rabbit, the formation of endogenous pyrogen is a necessary intermediate step between bacterial pyrogen and fever It is tempting to suppose that such an intermediate step is always necessary, but much work remains to be done before such a proposition can be either affirmed or denied The endogenous pyrogen most probably acts on certain cells in the central nervous system, modifying their behaviour in such a way that the effect of cold on the peripheral and central receptors is mimicked It may act on the vessels of the kidney, producing the peculiar changes already discussed, but this again is to go beyond the evidence

The considerable interval between the entry of endogenous pyrogen into the blood-stream and the onset of fever suggests the formation of a further intermediate substance The latent period may, however, represent the time taken for the endogenous pyrogen to pass from the blood plasma to the site of action in the cell, for its chemical properties indicate that it is a large molecule, and it may have a fair distance to travel

* * *

The function of hypothesis is to stimulate experiment, and these remarks are chiefly justified in that sense It must be clear to the reader that the problem of fever, hitherto so resistant to scientific inquiry, is now beginning minutes pyrogenic activity was always considerable Farr and LeQuire (1950) and LeQuire (1951) agreed but found that, when typhoid vaccine was incubated with citrated plasma before injection, the fever produced by its intravenous injection into recipient rabbits was hastened and augmented compared with that produced by incubating the pyrogen with saline solution They attributed the effect to aggregation of the vaccine, which protected it from removal by the reticulo-endothelial system Such are the observations from which the new developments in our understanding of fever stem

Before describing these experiments it is necessary to explain the difference between the tolerance and the immunity which occur after repeated injections of pyrogen If a given dose of pyrogen is injected daily, the amount of the fever (measured by the area of the curve of raised temperature) gradually lessens and after about a week or 10 days becomes small and thereafter remains unchanged The animal is said to be tolerant Left alone for 3 weeks and then reinjected, the animal gives a response which is equal in size to its original response The tolerance has disappeared

Now, pyrogens are chemically rather like antibodies polysaccharides are major constituents of both of them Tolerance is not, however, due to the formation of specific immune antibodies, for the following reasons (1) its rate of development during injection and its persistence after injection are not parallel to the amount of immune antibodies in the blood, and (2) it is not specific an animal that has become tolerant to a bacterial pyrogen derived from one species gives a reduced response to pyrogen derived from a related, but not identical, organism

With this digression we may return to our main theme The story has been developed by investigations in the rabbit and in man, and, since the facts elucidated differ materially in the two species, it will be necessary to treat them separately

Effect of Pyrogens in Rabbits

Using pyrogen derived from *Proteus vulgaris*, Grant and Whalen (1953) found that fever after intravenous injection began earlier (12 minutes) after large doses (5 µg upwards) than after smaller doses (26 minutes for 1 µg) These responses had an early peak and a later peak When large doses (100 µg) were injected intravenously, citrated blood withdrawn during the subsequent 3 hours was also pyrogenic when blood was withdrawn 60-180 minutes after injection, the febrile response was hastened and the secondary peak tended to be smaller or absent Grant and Whalen also showed that incubation of the pyrogen with citrated or heparinised plasma before injection diminished the latency of the ensuing fever They attributed these effects to the interaction between bacterial pyrogen and plasma, leading to the formation of a new and more rapidly acting endogenous pyrogen Grant (1953) showed that this capacity to form endogenous pyrogen is lost in the tolerant animal Thus incubation of pyrogen with plasma from normal animals produces an augmented and quickened response in tolerant recipients On the other hand, incubation of pyrogen with plasma from tolerant animals neither accelerates nor augments the response in tolerant recipients

These results have been confirmed and amplified by Atkins and Wood (1955)

They investigated the responses to typhoid vaccine in three groups of rabbits

(1) *Unsensitised* animals that had received no previous injection.

(2) *Sensitised* animals that had received one or two previous injections at intervals of not less than three weeks, with three to five weeks elapsing before the final test

(3) *Tolerant* animals injected intravenously daily for 7-8 days and tested within 24 hours of the last injection

Blood was withdrawn by cardiac puncture 5, 30, 60, and 120 minutes after intravenous *injection of the vaccine and allowed* to clot, 50-60 ml of serum warmed to 37°C was injected intravenously to recipient rabbits next day In the blood of the *unsensitised rabbits* the resulting fever indices (the areas enclosed by the curves of raised temperature) fell to half their initial value at 30 minutes and thereafter remained unchanged. In the *sensitised* rabbits the initial (5 minutes) value was less than half that of controls, and all pyrogenic activity had gone at 30 minutes, thereafter reappearing, the value at 90 minutes *being similar* to that at 5 minutes The blood of *tolerant* rabbits showed no significant activity at any time

As Grant and Whalen (1953) had found, the blood withdrawn at 120 minutes produced a more rapid response than that withdrawn at 5 minutes Atkins and Wood (1955) think that some of this secondary pyrogen may come from injured leucocytes, firstly because bacterial pyrogen produces a leucopenia which precedes the fever, and secondly because Braud et al (1955) have shown that a large part of injected *Esch coli* endotoxin quickly enters the buffy coat Atkins et al (1955) have also found that cortisone 50 mg daily suppresses fever but not leucopenia following the injection of typhoid vaccine, the serum of such rabbits contains as much transferable pyrogenic activity as that of rabbits untreated with cortisone Cortisone thus does not affect the action of pyrogen on blood but its later effect on the fever-producing process

These studies, and particularly those of Grant (1953), suggest that in the rabbit bacterial pyrogen produces in the blood-stream a secondary or endogenous pyrogen with a quicker action, and that plasma is the chief reactor with this bacterial substance

Another approach to the problem of fever in the rabbit has been that of Bennett and Beeson (1953a and b) As has been mentioned, these workers only obtained febrile responses from saline extracts of one normal tissue—namely, polymorphonuclear leucocytes The active material is thermolabile and non-dialysable, it produces no leucopenia or leucocytosis and exhibits no tolerance or cross-tolerance They suggest that this constituent of normal leucocytes may be the intermediate agent between bacterial infection and fever

However, some peculiar facts have not so far been fully explained

(1) The most convenient way of obtaining leucocytes is to inject physiological saline solution into the peritoneal cavity Both the leucocytes and the fluid in which they are suspended are pyrogenic yet the rabbits whence they are drawn have no fever As, in such *animals, the thoracic-duct lymph* and circulating blood contain no demonstrable pyrogenic activity (Bennett 1956b), it is concluded that the pyrogenic substance is not absorbed from the peritoneum

(2) Rabbits in which circulating granulocytes have been abolished by previous treatment with nitrogen mustard respond in the usual way with fever to injections of bacterial pyrogen, influenza virus, and various particulate materials In addition sterile peritoneal exudates produced by injection of physiological saline are pyrogenic even though they contain no leucocytes (Bennett and Beeson 1953b) It therefore seems that there may be a source other than leucocytes for pyrogenic substances, though Bennett (1956a) failed to find it by extracting tissues of leucopenic animals

(3) Injection of pneumococci into the peritoneal cavity produces high fever, yet intravenous or intraperitoneal injection of dead pneumococci produces none Like the sterile exudate, the peritoneal fluid induced by live pneumococci yields

continued with intervals of complete inertia, and the patient was finally delivered spontaneously of a macerated fœtus 110 hours after the membranes had been ruptured No gross abnormality was found *in the fœtus*

The 4 stillbirths in this series illustrate only too clearly one of the dangers of artificial rupture of the membranes as a method of induction of labour Labour failed to start for many hours or days, and then only with irregular and ineffective contractions During all this time the fœtus, perhaps already near the limit of its placental reserve, was subjected to an added measure of anoxia over a long period by the uterine retraction which followed the escape of the liquor amnii It is impossible to know what degree of anoxia was present before the interference was undertaken, or what degree of anoxia was due to the induction It seems likely, however, that it is just in those cases where oxygenation of the fœtal blood is becoming dangerously low that the risk of death from the added anoxia of the induction is so much the greater

If one can be wise after the event, it may be said that, in these four fatal cases, cæsarean section ought to have been done before the fœtus died when the course of labour proved to be so slow In this series of 68 inductions cæsarean section was done on 4 occasions for this very reason The difficulty is always to know in which case, and exactly when, to do this If caution were not exercised, it might be found, too often, that cæsarean section was done for failed induction rather than induction of labour for postmaturity

To say that 4 stillbirths in 68 surgical inductions of labour represents a fœtal mortality of nearly 6% may or may not be significant in the statistical sense of the word, but the figures certainly do not provide any basis for advocating the routine use of artificial rupture of the membranes in an attempt to avoid the dangers of postmaturity They ought, at least, to remind us that surgical induction of labour is not invariably successful, nor is it always safe for the fœtus

Attempts to induce labour with castor oil and enemata too often fail Although a failed "medical induction" is sometimes regarded as entirely harmless, it is often disappointing The moral effect of failure on the patient and her attendant may not always be without remote repercussions on subsequent events Inertia during labour is closely bound up with demoralisation of the patient or her obstetrician Induction of labour by the oxytocin-drip method has had many strong advocates, but among the patients here reported it was not used often enough to enable conclusions to be drawn

Conclusion

An attempt has been made to estimate the saving of infant life that could be achieved by preventing postmaturity Instead of considering gross fœtal and infant mortality-rates, the estimate of risk due to postmaturity has been based upon the incidence of fœtal and neonatal death from anoxia in circumstances which do not allow of any clear alternative explanation for the fatality On this basis it is possible to estimate the maximum possible loss of life that can be attributed to the postmaturity itself

In all the cases in which pregnancy passes the 41st week the loss directly due to postmaturity is less than 1 2%—possibly considerably less It probably varies from something less than 0 4% between the 41st and 42nd weeks to something less than 4 3% after the 44th week has been passed *In a midwifery practice with about 8500 viable births a perfect method of induction of labour used on 2600 occasions immediately before the 41st week of pregnancy was completed could not save more than 14 infant lives* Used on 115 occasions immediately before the 44th week was completed it could not save more than 2 infant lives

An appreciation of these figures is important before we are justified in advocating the routine avoidance of postmaturity by induction of labour with an imperfect method There is reason to believe that, in postmaturity, artificial rupture of the membranes carries with it dangers to the fœtus that are considerably greater than those which the interference is designed to circumvent The statistical studies that have come from Professor Baird's department in Aberdeen, and in particular the observations of Walker and Turnbull (1953) on fœtal blood oxygen content, have focused the attention of all practising obstetricians on the dangers of postmaturity

We must accept that postmaturity carries an increased risk to the fœtus, but this is not necessarily a good reason for forcing the fœtus out of frying-pan of postmaturity into the fire of induction of labour For those who think they have found a safe and effective method of induction there is not any problem For those who are impressed by the fallibility and the dangers of all the present-known methods of induction the management of postmaturity will remain a difficult problem Appreciation of the dangers of postmaturity is essential, but that must not overshadow an understanding of the dangers of induction

In the presence of other complicating factors the management of postmaturity calls for the fullest individual consideration, for all the niceties of judgment, and often also for finesse in treatment In uncomplicated cases, with our present imperfect methods of induction of labour, it is probably better to avoid the treatment of postmaturity altogether rather than to embark on a rigid policy of prevention

I wish to thank my colleagues at Queen Charlotte's Hospital for allowing me to make use of the clinical records of their cases

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THE CHECK-VALVE MECHANISM AND THE MEANING OF EMPHYSEMA

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> "We are therefore within sight of a rational concept of emphysema reasonably secure in its physiological support, but somewhat tentative in the links between structural and functional change" Arnott *(1956)*

This paper is written with the object of trying to strengthen these links

* * *

Chevalier Jackson (1930) gives a very clear account of bronchial obstruction in all its variations and the several effects that these produce He classifies obstructions into

1 *Complete blockage (corking), which leads to collapse of the* lung beyond the block as the trapped air is absorbed

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3 *Ball-valve obstruction,* which blocks inspiration but allows air to pass out during expiration This leads to collapse and atelectasis even more quickly than "corking

4 *Check-valve obstruction,* which allows air to be drawn in during inspiration but prevents it from passing out during expiration This leads to distension or emphysema of the lung beyond the valve

An obstruction situated on the junction of two bronchi may act as a ball valve in one and a check valve in the ther, and so give rise to atelectasis and emphysema in wo adjacent segments of lung Jackson's paper is based on observations with a bronchoscope He saw these effects produced by obstructions of several kinds foreign bodies, of which peanuts formed the majority, tumours, both benign and malignant, local swelling of the mucous membrane, and plugs of viscid mucus I am here primarily concerned with the check valve, but the other types of bronchial obstruction and their effects should not be forgotten

* * *

The simplest and most dramatic results of check-valve action are seen in the so-called balloon cysts, which may fill half the thoracic cavity and resemble tension pneumothorax None of those who describe them question their method of production On no other basis can one explain how they quickly fill up again with air under considerable positive pressure after aspiration, and at necropsy it has sometimes been possible to demonstrate their communication with a tiny bronchus (Koontz 1925, Miller 1926, Pearson 1930, Parmelee and Apfelbach 1931; Anspach and Wolman 1933, Miller 1933, Sellors 1938, Kaltreider and Fray 1939, Brown and Brock 1942) There can be no doubt, therefore, that check-valve action is a very potent mechanism in inflating terminal air sacs beyond their natural size Smaller cysts, single or in groups, may result from the same mechanism in a variety of other pathological states Examples are recorded under a number of different names—air cysts, caverns, blebs, bullæ, and focal emphysema—and as being associated with tuberculosis, pneumoconiosis, and staphylococcal pneumonia Asthma is often present as well

From whatever cause they arise and whatever the size or distribution of the cavities, the physiological effects as judged by analyses of blood and air are the same in all and similar to those found in "obstructive" pulmonary emphysema (Christie 1934, Hundato and Fray 1934, Kaltreider and Fray 1939) The air pressure within these cysts has sometimes been recorded In Brown and Brock's case it was -2 ± 2 cm H_2O and remained unaltered by the aspiration of several hundred ml of air In Kaltreider and Fray's case it was -6 ± 5 cm H_2O and the size of the cavity and the pressure were unchanged by aspirating two litres of air In Pearson's case the pressure was very much higher $+4-16$ cm in the cavity, while the initial pleural pressure found when inducing artificial pneumothorax was $-12-3$ cm Similar wide variations of pressure are found in spontaneous pneumothorax

It is only the unfortunate few that pump themselves up to desperately high levels In either condition a state of equilibrium, depending on the precise anatomy of the valve, is reached in every case If it closes completely as soon as the inspiratory effort ceases, the minimum pressure within the cavity will be about atmospheric, and the maximum reading will represent a balance between the expiratory pulmonary pressure on the retained air and the elastic tension of the surrounding lung The high positive readings reached by Pearson (1930) or found in tension pneumothorax could never be reached by the mere retention of air drawn in by inspiratory effort. If, however, the valve did not close completely during expiration, and the pressure in the larger cartilaginous air tubes was forced up by a cough against the resistance of a closed glottis, air could be forced into the cavity as in pumping up a tyre I think that it is in this way that the high positive pressures are produced The ingenious researches of Dayman (1951) threw considerable light on the many factors involved and led him to conclude that even in health the intrathoracic airways can behave as check valves to a slight degree during expiration, though the effect is very much greater in advanced emphysema when the elasticity of the lungs is impaired

The clinical course taken by these cavities is as varied as are the diseases that give rise to them and the nature and varying patency of their communication with the bronchi If the airway is cleared the cyst will collapse and disappear completely If check valve changes to ball valve or "corking," the cavity will be replaced by atelectasis With continued check-valve action the cyst may enlarge or remain stationary and clinically silent It may fill with clear mucus or infection may turn it into an abscess, which in turn may discharge and heal, resolve to form a fibrous scar, or persist as bronchiectasis These possibilities apply equally whether the cyst be large or minute

No great exception will probably be taken to what has been said so far, but it may not be so readily accepted that generalised hypertrophic emphysema is no more than the distension of every terminal air-sac into a tiny tension cyst by check-valve action, and that the disease-state that causes it is asthma Still less is it accepted that the presence of generalised emphysema is proof of a primary asthmatic state, though no other explanation has ever been put forward The reason for this reluctance is twofold, and as in so many controversies it arises mainly from limitations of nomenclature Asthma is a term reserved exclusively for the classical paroxysmal type Emphysema is a name given equally to a clinical picture and a pathological state, yet if we find the former it is by no means proof that the latter is also present

Although we limit the meaning of the term asthma in this way, the disorder can, in fact, range through every grade of severity from the classical paroxysmal attack to a disturbance so slight and chronic that it is often regarded as lying within the limits of normal health (Lister 1955) This slight and chronic form of asthma, for which we have no generally accepted name and which is very much more common than the paroxysmal, is also the form particularly prone to produce emphysema This view of the matter is of respectable antiquity, and was put forward very clearly by Laennec (1829), though he also was cramped, as we are, by having no generally accepted name for the minor grade He called it the "dry catarrh", and I cannot do better than quote from him at some length He says

> "This disease, when existing in a middling degree, frequently remains altogether latent for a long course of years, the subjects of it being no further conscious of its presence than observing that they are shorter of breath than others when they ascend an elevation or attempt to run After a time the dyspnœa comes on in fits which last usually several days and are so severe as to merit and obtain the name of asthma" Again, "The most common cause of dyspnœa when of sufficient severity to be termed asthma is a dry catarrh latent or manifest and emphysema of the lungs is the consequence of this" Again, "Pulmonary emphysema supervenes almost always to an extensive and severe dry catarrh, and nearly all the subjects of asthma from the last named disease, on examination after death, exhibit a greater or less dilatation of some of the bronchial cells These facts lead us to a simple explanation of the mechanism of dilatation of the air cells It has been already shown that in the dry catarrh, the smaller bronchial tubes are frequently completely obstructed, either by the pearly sputa or by the swelling of their inner membrane. Now, since the muscles of inspiration are numerous and powerful, while expiration, on the other hand, is produced merely by the elasticity of the parts and by the feeble contraction of the intercostal muscles [sic] it must frequently happen that the air, which during inspiration had overcome the resistance opposed to its entrance by the tumid state of the bronchial membrane and the sputa, is unable to force the same obstacles during expiration, and remains therefore imprisoned in the cells, by a mechanism somewhat similar to the valve of an air gun The succeeding inspirations, or at least such of them as are energetic, introduce a fresh supply of air into the same cells, and thereby necessarily occasion their dilatation and, provided the obstruction is of some continuance, the dilated condition of the cells will be rendered permanent. It follows from this view of the matter that the dry catarrh tends as naturally

continued with intervals of complete inertia, and the patient was finally delivered spontaneously of a macerated fœtus 110 hours after the membranes had been ruptured No gross abnormality was found in the fœtus

The 4 stillbirths in this series illustrate only too clearly one of the dangers of artificial rupture of the membranes as a method of induction of labour Labour failed to start for many hours or days, and then only with irregular and ineffective contractions During all this time the fœtus, perhaps already near the limit of its placental reserve, was subjected to an added measure of anoxia over a long period by the uterine retraction which followed the escape of the liquor amnii It is impossible to know what degree of anoxia was present before the interference was undertaken, or what degree of anoxia was due to the induction It seems likely, however, that it is just in those cases where oxygenation of the fœtal blood is becoming dangerously low that the risk of death from the added anoxia of the induction is so much the greater

If one can be wise after the event, it may be said that, in these four fatal cases, cæsarean section ought to have been done before the fœtus died when the course of labour proved to be so slow In this series of 68 inductions cæsarean section was done on 4 occasions for this very reason The difficulty is always to know in which case, and exactly when, to do this If caution were not exercised, it might be found, too often, that cæsarean section was done for failed induction rather than induction of labour for postmaturity

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In all the cases in which pregnancy passes the 41st week the loss directly due to postmaturity is less than 1 2%—possibly considerably less It probably varies from something less than 0 4% between the 41st and 42nd weeks to something less than 4 3% after the 44th week has been passed In a midwifery practice with about 8500 viable births a perfect method of induction of labour used on 2600 occasions immediately before the 41st week of pregnancy was completed could not save more than 14 infant lives Used on 115 occasions immediately before the 44th week was completed it could not save more than 2 infant lives

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Chevalier Jackson (1930) gives a very clear account of bronchial obstruction in all its variations and the several effects that these produce He classifies obstructions into

1 *Complete blockage (corking), which leads to collapse* of the lung beyond the block as the trapped air is absorbed

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4 *Check-valve obstruction*, which allows air to be drawn in during inspiration but prevents it from passing out during expiration This leads to distension or emphysema of the lung beyond the valve

while check-valve action remarkably prevents anything approaching a normal range of expiration He cannot empty his chest further because the air is trapped in the alveoli But if his bronchioles could maintain a normal calibre during expiration he would be able to empty his chest, and there is no reason, so far as this figure indicates, why his lungs should not then return completely to normal just as the local emphysema in one of Jackson's patients would after he had extracted the peanut Gough (1955) has shown that in the lungs of fatal cases of status asthmaticus there is no structural emphysema at necropsy, though one can be sure that if films had been taken of these patients shortly before death they would have revealed an even greater degree of distension than fig 2 Functional emphysema then is a completely reversible state entirely comparable to transient tension cysts, which vanish when the airway is reopened The more brief and infrequent the asthmatic attacks, the less likely are permanent structural changes to supervene, and vice versa

* * *

To produce structural emphysema, some additional factor is required to damage the tense alveolar meshwork In Flavell's (1952) opinion healthy alveoli cannot be ruptured by any physiological range of pressure Moolton (1935) showed that, if the alveolar meshwork had been damaged, pressures well within the physiological range could produce cavities which would not return completely to their original size when the pressure was relieved Gough also points out that emphysema is not found at necropsy in pure spasmodic status asthmaticus, but if chronic bronchitis (by which he presumably means infection) has been present as well, then structural emphysema is found post mortem Given time several factors can, alone or in combination, produce this damaging effect and, as it were, fix the terminal air-sacs in their distended condition As age advances, the skeleton becomes more rigid and the posture of habitual elevation of the ribs and bowed back becomes less and less easy to correct Adami and Nicholls thought that the capillaries might be compressed and so the blood-supply to the tense walls of the alveoli would be impaired This may be true Certain it is that as we grow older bodily structures tend to lose elasticity, and people vary greatly in the age at which these changes begin and in the organs most affected We know they can arise in the lungs and cause the so-called small-lunged or atrophic emphysema If a lung undergoing this degenerative process has been subject for several years to the check-valve action of chronic asthma or "dry catarrh", the classical picture of hypertrophic emphysema will be produced in its structural sense The lungs are bulky, pale, and dry, and have the feel of a feather pillow Microscopically the terminal air-sacs are seen to be distended, with thin, atrophic walls, many of which have ruptured so that adjacent alveoli coalesce Heavy smoking and living in polluted air, or the inhalation of noxious dusts, bring the risk of chemical and mechanical damage

Infection, however, is by far the most common and important damaging factor It so often dominates the clinical picture and compels the patient to seek our advice that we tend to regard it as the primary cause of the emphysema Infection also commonly dominates the pathological picture, as indeed it must, whenever it is present, seeing that purely functional emphysema leaves no post-mortem change But non-specific infection alone cannot produce generalised emphysema It is true that histologically in acute bronchopneumonia one can find areas in which their walls have ruptured and the alveoli have become confluent, and no doubt the same mechanisms have been at work to produce these changes as in more chronic illnesses It is also true, as already stated, that conditions of long standing—for instance, tuberculosis and pneumoconiosis—can produce tension cysts and areas of focal emphysema, but in these diseases the changes will be relatively gross and uneven in distribution Other parts of the lung will be collapsed from complete bronchial obstruction or consolidated or fibrotic from the primary pathological process By contrast the dilatation of and damage to the alveoli and bronchioles in "chronic bronchitis and emphysema" is spread relatively evenly throughout the whole of the lung parenchyma

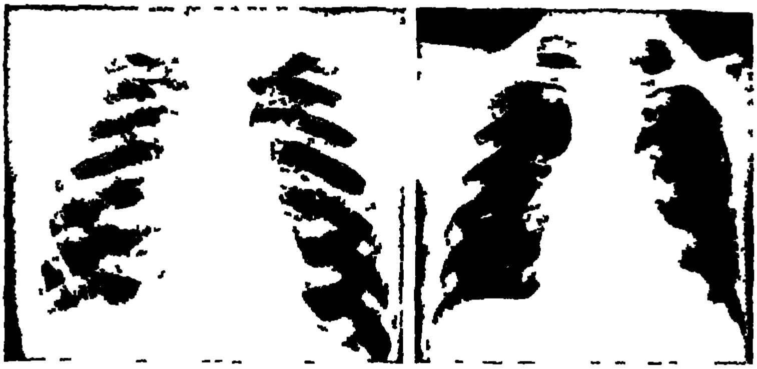
There are other reasons for suggesting that this disease is not primarily the result of infection The pathological picture is well described and illustrated by Reid (1954) She points out that the earliest change consists in an extension beyond the normal number and range of distribution of goblet cells and simple catarrh of the bronchial mucosa This entirely conforms to the natural history of the disease as observed clinically The more carefully we conduct our history-taking and examination, the more will we find evidence of a long-standing, constitutional, hereditary, or allergic state corresponding to Laennec's "dry catarrh" Other members of the family may have been asthmatic or bronchial There may be a history of hay-fever or frequent colds that start in the nose and later settle on the chest, or of winter and morning cough often attributed to smoking, all preceding the first recognisable onset of infection Many patients will distinguish between attacks of wheezing with thick, mucoid sputum, which they term asthma, and those with looser, yellow sputum, often associated with fever, which they term bronchitis

Precisely as one can trace in one's practice an unbroken range of cases through every grade of severity, from the mildest examples of dry catarrh to those in whom the entire respiratory tract is heavily and permanently infected, so one can observe in them the corresponding grade of emphysema from the reversible or functional to the permanent or structural The pathological picture also conforms As the catarrh and mucus secretion increases so will the mechanical effects of the bronchial obstruction increase These will not only be check valves There will also be partial blocks, corkings, and ball valves, to use Jackson's terms, all according to the precise site and degree of secretion and congestion at the moment, each producing its appropriate effect of emphysema, rhonchi, or atelectasis To these will be added the secondary effects of the inflammatory process, in the form of minute patches of pneumonia, and small abscesses, all in various stages of activity and resolution, which make up the full-blown picture described by Reid

* * *

Why does bronchitis become chronic in only an unfortunate minority ? Why do not all who dwell or work in polluted atmospheres develop emphysema ? And why do we find atrophic, small lungs in some and hypertrophic emphysema in others ? The reason must surely be that the lungs that develop emphysema are different They have reacted in a different way—in

to the production of emphysema of the lungs as the chronic mucous catarrh leads to dilatation of the bronchis ”



a b
Fig 1—Chest of normal man (a) inspiration, (b) expiration

This check-valve theory, as it may be termed, seems to have attracted little attention or support It was soon supplanted by the expiratory theory put forward in the first place by Mendelssohn (1845) and subsequently elaborated in the forceful writings of Jenner (1865) They believed that emphysema was caused by strong expiratory effort against resistance as in the expulsive effort of childbirth, glass-blowing, the playing of wind instruments, and particularly the constant coughing of sufferers from chronic bronchitis The theory was that during forced expiration the rigid portions of the thoracic cage—namely, the ribs—pressed on the underlying lung and forced air under pressure into those parts which were surrounded only by soft tissues, particularly around the apices and in the costophrenic angles The presence of universal emphysema was explained by the hypothesis that as the ribs moved up and down with respiration they forced the air from immediately beneath them into those portions of the lungs underlying the intercostal spaces The theory is easily illustrated by grasping a slightly inflated rubber balloon The fingers represent the ribs and the bubbles of rubber extruded between them represent the emphysema One may not think this a particularly convincing theory to have held the field for so long, but it still survives, if not quite in this form, in textbooks, and by implication in the commonplace diagnosis “ chronic bronchitis and emphysema ” Recently there appear to be signs of a return to Laennec’s theory

At the International Congress of Internal Medicine at Madrid last autumn Arnott (1956) referred to it and made the statement quoted at the beginning of this paper Previously Brodie and Dixon (1903) had been led by their pharmacological experiments to the conclusion that the asthmatic state was due to check-valve action from spasm of the bronchioles, which could be induced by vagus stimulation or drugs (pilocarpine) Adami and Nicholls (1910) refer to their work, and put forward the check-valve action of asthma as a satisfying explanation for the production of emphysema Norris and Landis (1924) mention the theory, but with no special emphasis, among several others current at that time heredity, occupation, chronic bronchitis, and premature ossification of costal cartilages

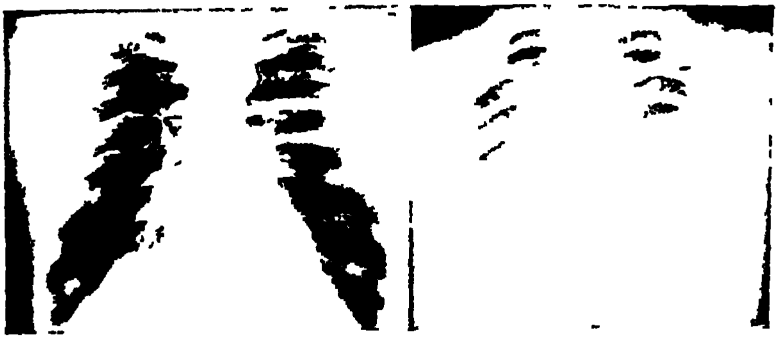
* * *

When one considers how many diseases can cause check-valve action, their ever-changing pattern, and the complications that may arise, one can well appreciate the difficulties of those who have sought to define and pin down a diagnosis of emphysema and to assess its severity by some clinical, radiological, or physiological formula based on a single examination

For instance, Fletcher (1952) compared the clinical opinion of eight physicians against a radiological diagnosis of emphysema The patients all had pneumoconiosis Knott and Christie (1952) found wide discrepancy between clinical and radiological diagnosis Donald (1953) made physiological tests on patients diagnosed as emphysematous on clinical and radiological grounds and found that there were too many variables (in sepsis, bronchospasm, and cardiac efficiency) to allow of close comparison Curtis (1955) made physiological tests on patients before thoracotomy and compared his findings with the presence or absence of emphysema in biopsy specimens In almost all his patients the operation was pneumonectomy for pulmonary tuberculosis Yet these papers formed the subject of a leading article (*Lancet* 1956) headed “ Hypertrophic Emphysema ”

Confusion will arise if we regard emphysema as a primary disease and one merely found in frequent association with other chest complaints, as so much of the literature on the subject seems to imply It is always secondary, and the result of check-valve action The number, size, and distribution of the distended air sacs depend on the primary pathological process producing the check valve, and may in fact constitute a valuable clue to its nature Thus, just as a balloon cyst or lobar emphysema (Cottom and Myers 1957) in a child suggests an abnormal bronchiole, or a group of tension cysts or area of focal emphysema may suggest tuberculosis, so universal distension indicates a condition that produces check-valve action uniformly throughout the lungs, and it is hard to think of an alternative to asthma that could do this

Again, to borrow Arnott’s terminology, emphysema may be functional or structural So far as it is functional it is potentially reversible, and it certainly will fluctuate widely in degree from time to time Figs 1 and 2 illustrate emphysema of this kind Fig 1 shows the chest of a healthy man aged 60 in maximum inspiration and expiration Fig 2 shows the corresponding films of a man complaining of increasing breathlessness on effort, typical of Laennec’s “ dry catarrh ” Here the diaphragm is depressed and flattened to a degree well below that which the most forcible normal inspiration can produce,



a b
Fig 2—Chest of man with emphysema (a) inspiration, (b) expiration

while check-valve action remarkably prevents anything approaching a normal range of expiration. He cannot empty his chest further because the air is trapped in the alveoli. But if his bronchioles could maintain a normal calibre during expiration he would be able to empty his chest, and there is no reason, so far as this figure indicates, why his lungs should not then return completely to normal just as the local emphysema in one of Jackson's patients would after he had extracted the peanut. Gough (1955) has shown that in the lungs of fatal cases of status asthmaticus there is no structural emphysema at necropsy, though one can be sure that if films had been taken of these patients shortly before death they would have revealed an even greater degree of distension than fig. 2. Functional emphysema then is a completely reversible state entirely comparable to transient tension cysts, which vanish when the airway is reopened. The more brief and infrequent the asthmatic attacks, the less likely are permanent structural changes to supervene, and vice versa.

* * *

To produce structural emphysema, some additional factor is required to damage the tense alveolar meshwork. In Flavell's (1952) opinion healthy alveoli cannot be ruptured by any physiological range of pressure. Moolton (1935) showed that, if the alveolar meshwork had been damaged, pressures well within the physiological range could produce cavities which would not return completely to their original size when the pressure was relieved. Gough also points out that emphysema is not found at necropsy in pure spasmodic status asthmaticus, but if chronic bronchitis (by which he presumably means infection) has been present as well, then structural emphysema is found post mortem. Given time several factors can, alone or in combination, produce this damaging effect and, as it were, fix the terminal air-sacs in their distended condition. As age advances, the skeleton becomes more rigid and the posture of habitual elevation of the ribs and bowed back becomes less and less easy to correct. Adami and Nicholls thought that the capillaries might be compressed and so the blood-supply to the tense walls of the alveoli would be impaired. This may be true. Certain it is that as we grow older bodily structures tend to lose elasticity, and people vary greatly in the age at which these changes begin and in the organs most affected. We know they can arise in the lungs and cause the so-called small-lunged or atrophic emphysema. If a lung undergoing this degenerative process has been subject for several years to the check-valve action of chronic asthma or "dry catarrh", the classical picture of hypertrophic emphysema will be produced in its structural sense. The lungs are bulky, pale, and dry, and have the feel of a feather pillow. Microscopically the terminal air-sacs are seen to be distended, with thin, atrophic walls, many of which have ruptured so that adjacent alveoli coalesce. Heavy smoking and living in polluted air, or the inhalation of noxious dusts, bring the risk of chemical and mechanical damage.

Infection, however, is by far the most common and important damaging factor. It so often dominates the clinical picture and compels the patient to seek our advice that we tend to regard it as the primary cause of the emphysema. Infection also commonly dominates the pathological picture, as indeed it must, whenever it is present, seeing that purely functional emphysema leaves no post-mortem change. But non-specific infection alone cannot produce generalised emphysema. It is true that histologically in acute bronchopneumonia one can find areas in which their walls have ruptured and the alveoli have become confluent, and no doubt the same mechanisms have been at work to produce these changes as in more chronic illnesses. It is also true, as already stated, that conditions of long standing—for instance, tuberculosis and pneumoconiosis—can produce tension cysts and areas of focal emphysema, but in these diseases the changes will be relatively gross and uneven in distribution. Other parts of the lung will be collapsed from complete bronchial obstruction or consolidated or fibrotic from the primary pathological process. By contrast the dilatation of and damage to the alveoli and bronchioles in "chronic bronchitis and emphysema" is spread relatively evenly throughout the whole of the lung parenchyma.

There are other reasons for suggesting that this disease is not primarily the result of infection. The pathological picture is well described and illustrated by Reid (1954). She points out that the earliest change consists in an extension beyond the normal number and range of distribution of goblet cells and simple catarrh of the bronchial mucosa. This entirely conforms to the natural history of the disease as observed clinically. The more carefully we conduct our history-taking and examination, the more will we find evidence of a long-standing, constitutional, hereditary, or allergic state corresponding to Laennec's "dry catarrh". Other members of the family may have been asthmatic or bronchial. There may be a history of hay-fever or frequent colds that start in the nose and later settle on the chest, or of winter and morning cough often attributed to smoking, all preceding the first recognisable onset of infection. Many patients will distinguish between attacks of wheezing with thick, mucoid sputum, which they term asthma, and those with looser, yellow sputum, often associated with fever, which they term bronchitis.

Precisely as one can trace in one's practice an unbroken range of cases through every grade of severity, from the mildest examples of dry catarrh to those in whom the entire respiratory tract is heavily and permanently infected, so one can observe in them the corresponding grade of emphysema from the reversible or functional to the permanent or structural. The pathological picture also conforms. As the catarrh and mucus secretion increases so will the mechanical effects of the bronchial obstruction increase. These will not only be check valves. There will also be partial blocks, corkings, and ball valves, to use Jackson's terms, all according to the precise site and degree of secretion and congestion at the moment, each producing its appropriate effect of emphysema, rhonchi, or atelectasis. To these will be added the secondary effects of the inflammatory process, in the form of minute patches of pneumonia, and small abscesses, all in various stages of activity and resolution, which make up the full-blown picture described by Reid.

* * *

Why does bronchitis become chronic in only an unfortunate minority? Why do not all who dwell or work in polluted atmospheres develop emphysema? And why do we find atrophic, small lungs in some and hypertrophic emphysema in others? The reason must surely be that the lungs that develop emphysema are different. They have reacted in a different way—in a word they are “ allergic ” (for that is all that this term means) and subject in some degree to the chronic, dry catarrh of Laennec and the check-valve action that this state applies

The lungs of these people present a constantly shifting pattern depending on fluctuations in the asthmatic state, variations in degree of infection, and the process of ageing Occupation, environment, and the efficiency of the cardiovascular system all have an additional and indirect bearing Thus at any given moment the degree of emphysema demonstrable by radiography or at the bedside will be in part functional or reversible because of check-valve action, and in part structural or irreversible from breakdown of the alveolar meshwork

One may make a more or less shrewd estimate of the relative proportions of these two elements (the functional and the structural) from the history and clinical picture In an elderly patient with rigid chest, inelastic skin, and hardened arteries, who has suffered for years from attacks of “ bronchitis ” with purulent sputum or has lived and worked in a polluted atmosphere, one would naturally expect the condition to be largely irreversible, the results of treatment meagre and the prognosis correspondingly poor In younger subjects with a more spasmodic history, little or no infection, and otherwise good general health and environment, the functional element might be expected to predominate On such a view one can readily understand—indeed one would expect—the poor results obtained with ephedrine and aminophylline in emphysema (Whitfield et al 1950, 1951) No drug could alter a condition due entirely to structural damage The observations were made when no bronchospasm was present Clinical details of the patients were not given, but the authors say that they were not clinically asthmatic and that there was nothing to suggest that asthma had been the cause of their ventilatory insufficiency Laennec might, however, have regarded them as subject to “ dry catarrh ”

Summary

Emphysema is never a primary disease, but always secondary

It is a state of over-distension of the terminal air-sacs of the lungs by check-valve action in the small bronchi or bronchioles A variety of conditions can cause this

Tension cysts or focal emphysema arise from the partial obstruction of one or a few bronchioles

Generalised emphysema results *only from asthma*—particularly from its minor and chronic form, rather than from the classical paroxysmal type

Functional emphysema is the distension of healthy alveoli by check-valve action It can be completely relieved by the removal of the obstruction

Structural emphysema is the irreversible state resulting from damage to the over-distended alveolar meshwork by secondary factors

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EFFECTS OF PENICILLAMINE AND DIMERCAPROL ON TURNOVER OF COPPER IN PATIENTS WITH WILSON'S DISEASE

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IT is now established that in patients with Wilson's disease (hepatolenticular degeneration) there is an inability to synthesise the copper-binding serum-protein cæruloplasmin, and copper therefore accumulates in the body, chiefly in the brain and liver Associated with these phenomena are an increased excretion of copper in the urine and a low level of copper in the plasma Moreover 60–80% of the serum-copper is “ direct reacting”—i e, not bound to cæruloplasmin—in contrast to healthy people, in whom only about 10% of the copper is not protein-bound The evidence for these observations has been reviewed by one of us (Walshe 1957)

Studies with radioactive copper (^{64}Cu) (Earl et al 1954, Bearn and Kunkel 1955, Bush et al 1955) have shown that, in healthy people, the copper is rapidly removed from the plasma, to reappear about twelve hours later bound to cæruloplasmin In patients with hepatolenticular degeneration this rapid fall and secondary rise do not take place, the ^{64}Cu level falling slowly but steadily during the period of study The patients with Wilson's disease excreted a higher percentage of ^{64}Cu in the urine and far less in the stools than did the healthy people

Hitherto the most effective treatment for patients with Wilson's disease has been to remove copper from the body with repeated courses of intramuscular dimercaprol (Denny-Brown and Porter 1951) In cases which are not resistant to this treatment and in patients who do not become sensitive to dimercaprol significant improvement may take place (Bearn 1956) Penicillamine hydrochloride by mouth in doses up to 1 5 g daily may be more effective than dimercaprol in promoting cupruresis (Walshe 1956, Bearn 1957)

In the present study the efficacy of dimercaprol and penicillamine in increasing the excretion of intravenously injected ^{64}Cu were compared The number of experiments

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was limited to a minimum to avoid giving unnecessary doses of a radioactive material to adolescents The opportunity was taken to make surface counts over the body to try and determine the site of concentration of the isotope after injection

Methods

The studies were made on one healthy male, aged 22, and on three patients with Wilson's disease Two of these have been reported previously (Walshe 1956, cases 3 and 5), and the third was a boy aged 18, who had the typical disease with a history of three years' tremor and slurred speech All three patients had difficulty in providing urine to a strict time schedule, but only two specimens were lost during the experiments (see figures)

The chemical method of estimating copper was that described by Earl (1954) and modified for greater accuracy by Walshe (1956)

Since inorganic salts of copper are toxic, it was important that the mass of copper used should be as small as possible A method was developed by Payne et al (1957) at the A E R E, Harwell, for producing copper of very high specific activity which at the time of injection had a mass of 1–3 μg of Cu for an activity of 100 μC The urine was assayed for radioactivity by counting samples dried in planchettes, as described by Anderson et al (1956), with a G E C type EHM 2 end-window Geiger-Müller tube The tube was standardised by counting a planchette containing a known fraction of the original ^{64}Cu

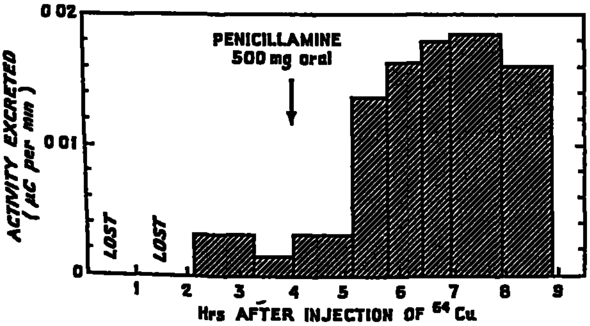

Fig 1—Excretion of ^{64}Cu by case 1 First two specimens of urine were lost.

For external counting of the liver a sensitive scintillation counter with a thallium-activated sodium-iodide crystal was used This was adjusted against constant skin markings by the technique of Riddell et al (1957)

Results

In the pilot experiment made on case 1 after the injection of ^{64}Cu, the first specimen of urine was lost, but by four hours the rate of excretion was 0 0015 μC a minute At this point she was given penicillamine 500 mg by mouth, and thereafter there was a steady increase in activity secreted until at eight hours she was excreting ^{64}Cu at 0 0186 μC a minute, a twelvefold increase (fig 1)

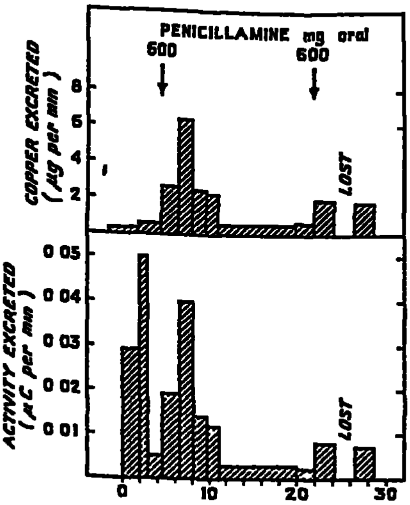

Fig 2—Excretion of copper by case 2. One specimen of urine at about 23 hours was lost

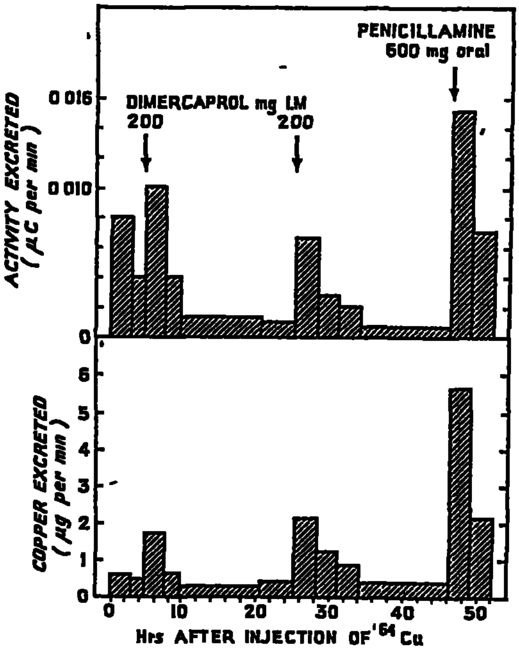

Fig 3—Excretion of copper by case 3

In case 2 the excretion of copper was determined both by radioactive and by chemical methods for twenty-nine hours after the injection of ^{64}Cu 100 μC During this time he was given penicillamine 600 mg by mouth at four hours and again at twenty-two hours As in case 1, the excretion of ^{64}Cu had *diminished to 0 005 μC a minute by four hours* After the first dose of penicillamine it increased to a maximum of 0 04 μC a minute and did not return to the resting value for nearly eight hours During this time 8 52 μc was excreted, if the initial rate had been maintained throughout, the amount would have been 1 92 μC Following the second dose of penicillamine at twenty-two hours there was again an immediate increase in the radioactivity of the urine (fig 2)

The urinary excretion of copper determined by chemical means shows a close correspondence over this twenty-nine hour period, except that the initial high excretion of ^{64}Cu is naturally not reflected by the excretion of non-radioactive copper The increase of excretion due to penicillamine occurs at the same point in the time scale and is of very similar magnitude on each occasion During the eight hours after the first dose of *penicillamine* 1300 μg of copper was excreted, at the base-line rate the excretion would have been 200 μg The

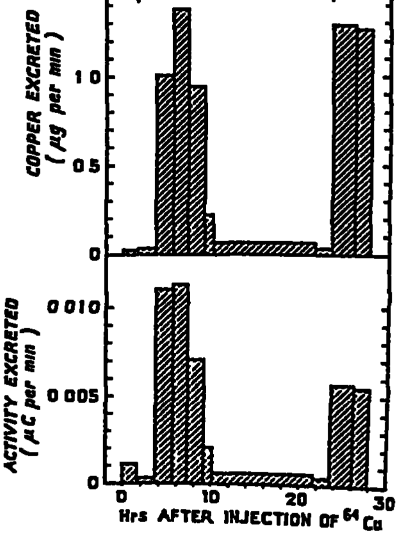

Fig 4—Excretion of copper by healthy man.

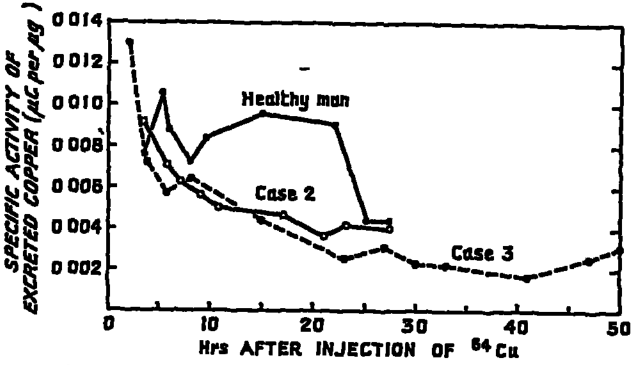

Fig 5—Variations in specific activity of excreted copper

figures available for the second peak also corresponded closely with the results obtained by radioactive assay

Case 3 showed the same immediate considerable excretion of ^{64}Cu as did case 2 Clearly it had not reached a base-line when he was given intramuscular dimercaprol 200 mg at four hours This, however, increased the excretion of ^{64}Cu to a maximum of 0 01 μC a minute, an increase of about four times the calculated base-line The excretion of ^{64}Cu during the period of the cupruresis was 2 5 μC compared with a theoretical excretion of 0 75 μC if dimercaprol had not been given A second injection of dimercaprol at twenty-five hours had an effect almost exactly like that of the first, with a total excretion of 2 13 μC against a calculated 0 58 μC for the period At forty-six hours penicillamine 600 mg was given by mouth This was followed by an increase in excretion of ^{64}Cu from 0 00065 μC a minute to a peak of 0 015 μC a minute—a twenty-fold rise, compared with increases of four and six for dimercaprol

The excretion of copper studied by chemical methods showed a similar picture, with an increase in the cupruresis of five-fold for each of the two injections of dimercaprol and one of fourteen-fold for penicillamine (fig 3)

Finally, a healthy man was studied by a similar experimental procedure He was given two oral doses of penicillamine, each of 600 mg, at four hours and at twenty-four hours The excretion of ^{64}Cu reached a peak of 0 0123 μC a minute after the first dose Calculated from the area of the peak this is a forty-seven-fold increase above the base-line However, after the second dose the peak was only nineteen times the base-line These values compare with increases of 48 and 44 times for copper determined by the chemical method (fig 4)

In cases 2 and 3 with hepatolenticular degeneration the specific activity * of the copper in the urine decreased steadily, whereas in the healthy man it stayed high for about twenty-four hours before decreasing to a value similar to that found in the two patients (fig 5) The significance of this is discussed below

Surface counts were made on case 3 and on the healthy man These showed that, while there was sufficient activity to estimate, the only site of concentration of injected ^{64}Cu was the liver In the healthy man 95% of the injected ^{64}Cu was located in the liver at ten hours, and thereafter there was a steady decline to 70% at fifty hours In case 3 there was never more than 40% of the ^{64}Cu present in the liver, and the variations of liver activity observed after the doses of the sequestrating agents are of very doubtful significance (fig 6)

The results are summarised in the accompanying table

Discussion

The original intention of this work was not to study the differences in copper metabolism between the healthy and patients with Wilson's disease, though this was in fact demonstrated by a comparison of the response of these two groups to penicillamine at four hours and at twenty four hours

In the healthy man there was a forty-seven-fold increase in the excretion of ^{64}Cu at four hours but only twenty-fold at twenty-four hours Presumably by this time much of the ^{64}Cu had become bound to cæruloplasmin and was no longer available for excretion In Wilson's disease, on the other hand, the response to penicillamine did not show this decrease (case 2, thirteen-fold at four hours, case 3, twenty-one-fold at forty-six hours) Presumably since the copper does not become protein-bound it remains freely available for excretion throughout the period of study

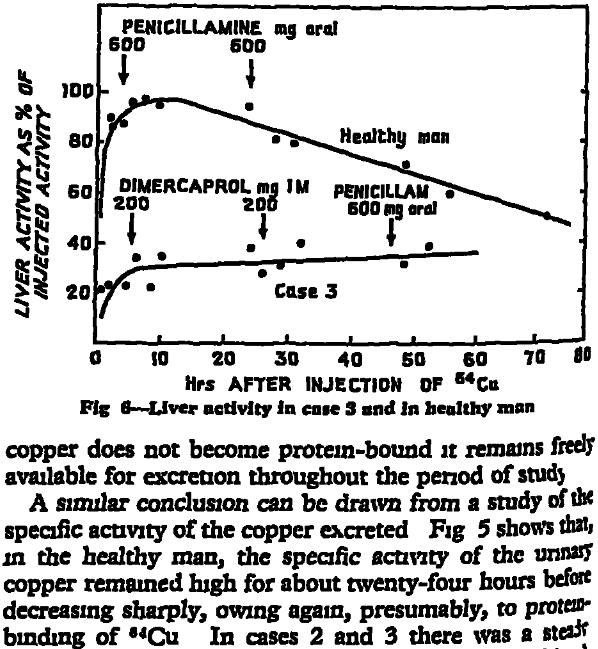

Fig 6—Liver activity in case 3 and in healthy man

A similar conclusion can be drawn from a study of the specific activity of the copper excreted Fig 5 shows that, in the healthy man, the specific activity of the urinary copper remained high for about twenty-four hours before decreasing sharply, owing again, presumably, to protein-binding of ^{64}Cu In cases 2 and 3 there was a steady decline in specific activity as the ^{64}Cu became diluted throughout the body pool The external body-counters also revealed the metabolic abnormality in the patient studied In the healthy control more than 90% of the injected copper was concentrated in the liver at ten hours, but in the patient only 40% of the copper was so concentrated

It might at first appear surprising that the healthy man had a greater percentage increase in copper excretion after penicillamine than had any of the patients, but it must be remembered that the resting excretion was extremely small, and the peak excretion never approached the very high values observed in Wilson's disease

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* The specific activity is calculated by dividing the activity of copper excreted in μC a minute by the quantity in μg a minute It has nothing to do with absolute quantities of metal

Person	Excretion of copper (μg a minute)					Excretion of ^{64}Cu (μC a minute)					
	Resting	After penicillamine	Times greater*	After dimercaprol	Times greater*	Resting	After penicillamine	Times greater*	After dimercaprol	Times greater	Total ^{64}Cu excreted
Healthy man	0 026	1 37	× 48	—	—	0·0002	0·0123	× 47	—	—	5 7 μC in 28 hr
	0 031	1 28	× 44	—	—	0 00028	0 0057	× 19	—	—	
Case 1						0 0015	0·0186	× 12	—	—	4 2 μC in 9 hr
Case 2	0 54	6 36	× 12	—	—	0·003	0·010	× 13			19 μC in 29 hr
Case 3	0 54			1 7	× 3	0·0025			0·010	× 4	11 5 μC in 52 hr
	0 38			2 1	× 5 5	0 0010			0 0066	× 6 6	
	0 30	5 6	× 14	—	—	0 0007	0·015	× 21			

* The increase is calculated from the area of the peak, not from the height

One other point very clearly shown by these experiments is that penicillamine is a very powerful agent for the mobilisation of body-copper, and that the increased copper which appears in the urine is released from body stores and has not been carried through from the gut There is also support for the view that penicillamine is more active than dimercaprol in this respect

Summary

The excretion of an injected dose of 100 μC of ^{64}Cu was studied in one healthy man and three patients with Wilson's disease together with the effect of oral penicillamine and intramuscular dimercaprol

The results show clearly that penicillamine is very active in promoting the excretion of copper and appears to be superior to dimercaprol in this respect There is good correspondence between the chemical and radioactive determinations of urinary copper

The bulk of the injected copper was concentrated in the liver by ten hours in the healthy man, reaching a maximum of more than 90% and then decreasing steadily to 70% by fifty hours, whereas in Wilson's disease the greatest concentration in the liver never exceeded 50%

Study of the specific activity of the copper in the urine supports the theory that, in healthy people almost all the injected copper becomes firmly bound to protein by twenty-four hours, whereas in patients with Wilson's disease it mixes with a large body pool of copper and remains readily available for excretion at the glomerulus

We wish to thank Dr Michael Ashby, Dr H Kryszek, and Dr S Nevin for permission to study patients under their care, Mr B R Payne and his associates at the Atomic Energy Research Establishment, Harwell, for their invaluable help in supplying copper of very high specific activity, and Dr W P Kennedy, of the Distillers Company (Biochemicals) Ltd, for a most generous gift of penicillamine.

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THE CLINICAL SIGNIFICANCE OF STERNAL TENDERNESS

THE VALUE OF SELECTIVE MARROW BIOPSY IN MALIGNANT DISEASE

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BONE tenderness in hæmopoietic disorders is well known (Wintrobe 1946, Witts 1946, Whitby and Britton 1953), and may affect any bone, most commonly the sternum, particularly in leukæmia, polycythæmia, and myelomatosis Less attention has been paid to the occurrence of bone tenderness in association with metastatic neoplasms and reticuloses, although some workers have reported that diagnostic material may be aspirated more regularly from tender than from non-tender bone

CORRELATION BETWEEN DIAGNOSIS AND STERNAL TENDERNESS IN 200 CASES

Diagnosis	No of cases in which sternal tenderness was	
	Present	Absent
Carcinoma malignant cells present in marrow film	15	2
Carcinoma malignant cells not found in marrow films	1	22*
Myeloid reticulosis	6	0
Reticuloses without evidence of marrow involvement	0	5
Myelomatosis	6	5
Plasmacytoma, apparently solitary, with normal bone-marrow	0	3
Acute leukæmia	5	7
Chronic leukæmia	1	9
Polycythæmia vera	2	2
Myelofibrosis	0	3
Megaloblastic anæmia	15	22
Other ' primary " cytopenia	3	6
Hæmolytic anæmias	0	7
Iron-deficiency and miscellaneous anæmias	7	46
Total	61	139

* 2 of these cases were found at necropsy, one and four weeks later, to have marrow metastases In 1 case the sternal-puncture needle had been inserted between two nodules of growth

Whitby and Britton (1953) and Lopes Cardozo (1954) recommend puncture of tender bone in the diagnosis of secondary carcinoma

Amy and Jaimet (1953) and Jaimet and Amy (1956) emphasise the importance of selective puncture of tender bone in patients presenting diagnostic problems, and report the finding of tumour cells in the marrow in unsuspected cases of neoplasm

Varadi (1955) found Sternberg-Reed cells in the marrow of five patients with Hodgkin's disease by "aimed" puncture of tender parts of the sternum This degree of success is in sharp contrast to that of other writers on the subject (Cooper and Watkins 1949, Baryd et al 1954)

Marrow puncture, however, is still generally done as a blind biopsy of either the iliac crests or the upper part of the sternum Although this is satisfactory in the diagnosis of hæmopoietic disorders it probably accounts for the comparative rarity with which neoplasms are diagnosed by marrow examination

Method

To assess the frequency and significance of tenderness 200 consecutive patients about to undergo marrow puncture were examined for tenderness of the sternum The bone was palpated from the manubrium downwards, firm pressure being made with the ball of the index finger Many healthy people complain of discomfort over the lower third of the sternum when examined by this method, therefore tenderness was regarded as present only if it was very definite Most of the patients who experienced tenderness on palpation also complained of pain on light percussion of the sternum, but the tenderness was elicited less constantly in this way

Marrow was aspirated from these tender spots or, if tenderness were absent, from the sternum at the junction of its upper two-thirds and lower third

Results

Of the 200 patients 61 were considered to have tenderness of the sternum In most cases the tenderness was quite sharply localised to small areas, usually in the lower third of the sternum Diffuse sternal tenderness was seen in a few cases of metastatic carcinoma, myelomatosis, acute leukæmia, and, most noticeably, in 4 of 6 patients with myeloid reticulosis as defined by Israëls (1951) In these patients generalised bone tenderness and spontaneous bone pain were usual

The diagnoses and presence or absence of sternal tenderness in the 200 patients is summarised in the accompanying table

Although sternal tenderness was found, as expected, to be common in patients with neoplastic blood disorders and in those with bone-marrow metastases, it was not confined to these groups of patients, nor was it found as often as expected in patients with leukæmia or with myelomatosis In the megaloblastic anæmias sternal tenderness was found only in severely anæmic patients, it disappeared with successful treatment, as in the leukæmias, but very much more rapidly, usually being absent after three or four days and indicating improvement in advance of the rise in hæmoglobin level, sometimes even before the reticulocytosis began The patients with non-hæmopoietic malignant disease studied did not form a representative sample of all such cases in the hospital being biased in favour of cases with known or suspected metastases in the marrow Even so, selective puncture of tender areas of bone proved of diagnostic value in some instances

Illustrative Case-reports

Case 1.—A man, aged 60, with carcinoma of the prostate, developed refractory normochromic anæmia No primitive cells were found in his peripheral blood Radiography of his skeleton showed no evidence of metastases in bone The acid and alkaline phosphatase levels in the serum were normal The blood-urea level was 80 mg per 100 ml, and it was thought that the anæmia might be secondary to renal impairment, but puncture of a tender sternum revealed clumps of carcinoma cells Simultaneous puncture of the non-tender left iliac crest yielded normal marrow

Case 2.—A man, aged 47, was admitted to hospital for the investigation of sciatica Radiography showed collapse of a lumbar vertebra, and the peripheral blood showed leuco-erythroblastic anæmia A diagnosis of secondary carcinoma was considered, but no primary growth was found Marrow aspirated from a sharply localised tender area of the sternum showed masses of abnormal reticulum cells, yet simultaneous puncture 1 cm above the tender spot yielded normal marrow The diagnosis of myeloid reticulosis was confirmed at necropsy

Case 3—A woman, aged 76, was admitted to hospital for the investigation of cervical lymphadenopathy She had no anæmia, but her peripheral blood showed neutrophil leucocytosis Lymph-node biopsy showed a necrotic tumour on which no firm opinion could be given The sternum and ribs were tender, and metastatic carcinoma was diagnosed by sternal puncture Necropsy disclosed a small carcinoma of the stomach with metastases in lymph-nodes, liver, and bones

Conclusions and Summary

Bone tenderness, in particular sternal tenderness, may develop in patients with various disorders but is particularly common in those with bone-marrow metastases and those with myeloid reticulosis

Selective puncture of tender bone will improve the chances of finding abnormal cells in such cases

Selective puncture of the marrow is recommended in the investigation of obscure cases, particularly if unexplained anæmia, bone destruction, or lymphadenopathy is present

It is a pleasure to thank Dr George Discombe for his advice and for his criticism of this paper

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SEX REVERSAL:

OVARIAN TISSUE ASSOCIATED WITH MALE NUCLEAR SEX

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The syndrome of gonadal dysgenesis, Turner's syndrome, is now a well-recognised, although uncommon, disorder of sexual development In its classical form it is characterised by female (or near female) bodily habitus, atrophic gonads, absence of secondary sex characters, amenorrhœa, and increased urinary excretion of pituitary gonadotrophic hormones Often there are associated congenital defects—notably short stature, webbing of the neck, and cubitus valgus The principal anomaly is in the gonads, which are represented only by a primitive genital ridge consisting of connective tissue and a few mesonephric remnants (Wilkins and Fleischmann 1944, Grumbach et al 1955)

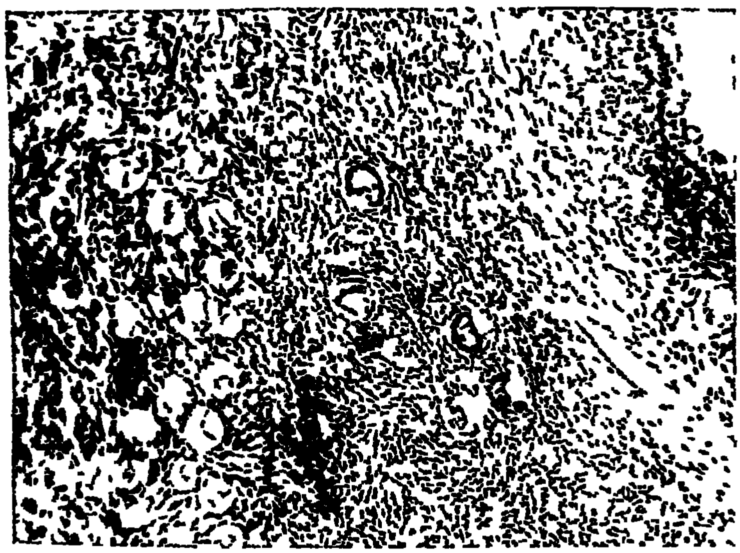
Recently it has become possible to determine the "genetic" sex of an individual by examining the cell nuclei of the skin (Moore, Graham and Barr 1953) and of the buccal mucosa (Moore and Barr 1955) Though it has not been rigidly proved that the chromatin bodies seen in a high proportion of the cells of normal females are the XX-chromosome complex, the presence of these bodies is generally held to indicate the female genotype (Lennox 1956) These tests of genetic sex have been applied to many people with Turner's syndrome, and it has been found, in most cases, that the epithelial cells are chromatin-negative—i e, that the genetic sex is probably male (Polani, Hunter, and Lennox 1954, Grumbach et al 1955) This view is upheld by this syndrome's association with coarctation of the aorta, a congenital anomaly normally largely confined to males, and by the observation (Polani, Lessof, and Bishop 1956) that 4 of 25 patients with Turner's syndrome had anomalies of red-green colour-vision, a defect inherited as a sex-linked recessive characteristic and ten times commoner in males than in females

The case we report here may be discussed within the general framework of Turner's syndrome but presents certain anomalous features and shows a much closer analogy with the syndrome of testicular agenesis (Klinefelter et al 1942)

Case-report

An only child was referred to Alder Hey Children's Hospital at the age of 10 days because of doubts about the "true sex" The baby had labia majora and minora and a phallus suggestive of an enlarged clitoris on which there was a hypospadiac urethral opening through which urine passed In front of the anus was a vagina with a second urethral opening on its anterior wall It was found subsequently that a single urethra left the bladder but divided into two after a short course Otherwise the baby, though small, was apparently normal, with no evidence of cardiovascular or skeletal abnormalities The bone age at 18 months corresponded to the chronological age The urinary excretion of 17-ketosteroids, determined on three occasions in the first 9 months, was 0 64, 0 22, and 0 25 mg daily These results are within the normal range for this age (Wilkins et al 1955)

Laparotomy at 17 months of age revealed a uterus and fallopian tubes of normal size The two ovaries, in their normal position, were slightly enlarged and cystic There was no sign of testicular tissue retroperitoneally or in the inguinal canals or



Biopsy of ovary at one edge can be seen part of the wall of a follicular cyst, while the remainder of the tissue shows many oogonia and immature graafian follicles (Hæmatoxylin and eosin ×110)

of any definite structures of wolffian origin A small piece of the right ovary was removed for microscopy Sections showed that the specimen contained a follicular cyst and that many oogonia were present, although formed graafian follicles were few (see figure)

Other investigations —Smears of the buccal mucosa were taken from both sides of the mouth on four occasions and were examined for the presence of " sex chromatin " A skin biopsy was similarly examined In every instance the proportion of cells showing the " sex chromatin " was less than 6%, a figure well below the lower limit seen in normal females Blood-films were also examined for " drumsticks " in the polymorphonuclear leucocytes (Davidson and Smith 1954) Three separate films were examined, and in each more than six " drumsticks " were seen in an examination of five hundred cells

Follow-up —At the age of 20 months the child was thriving

Discussion

This case presents several unusual features Clinically the appearance was of a female infant with an enlarged phallus She could therefore be regarded as a case of female pseudohermaphroditism Examination of the skin and buccal mucosa revealed that the nuclear sex was male, and that she should therefore be considered as a case of Turner's syndrome with enlargement of the phallus (Grumbach et al 1955) The finding of a female frequency of " drumsticks " on the polymorphonuclear leucocytes need not be regarded as invalidating the diagnosis of the genetic sex from the epithelial cells Ashley (1957) has shown that the sex-chromatin mass on the nuclear membrane and the " drumstick " on the polymorphonuclear leucocyte are not identical, and similar discrepancies have been seen in other cases of gonadal dysgenesis (Greenblatt 1957)

The histological appearances of the ovary present a much more serious discrepancy This case is the only one which can be traced in which the gonad of an individual of male nuclear sex shows the histological features of an ovary, all the usual structures of the ovary, including germinal elements, are present

Female Pseudohermaphroditism

The diagnosis of female pseudohermaphroditism must be considered first This condition is seen in adrenal cortical hyperplasia (Broster et al 1953) when the adrenal glands produce excessive amounts of androgenic hormones causing masculinisation of the female and precocious virilism Such persons are of female nuclear sex The present patient showed no evidence of virilism, she had no growth of sexual hair, and her excretion of urinary 17-ketosteroids was within normal limits for her age There is also a group of female pseudohermaphrodites without adrenal hyperplasia Few recent reports of this condition have been made Armstrong (1955) included 2 cases in a review of diversities of sex and found that the nuclear sex in both was female

Turner's Syndrome

The occurrence of individuals of male genotype—i e , absence of the sex-chromatin body from the resting nuclei of the cells of the skin and buccal mucosa—with female phenotype, female bodily habitus, and internal genitalia arising from the mullerian ducts, is now well recognised Most of these cases belong to the group usually called Turner's syndrome, the main features of which are outlined above, and usually show no evidence of masculinisation except for the few instances in which there has been enlargement of the phallus, 3 such cases have been reported recently (Gordan et al 1955, Grumbach et al 1955) in which laparotomy and section of the gonad showed the usual spindle-celled connective-tissue stroma and mesonephric remnants of the gonad of Turner's syndrome together with the presence of nests of " Leydig " cells in the medullary regions These cells have been recorded in the gonad of cases of the syndrome without enlargement of the clitoris, yet clitoral hypertrophy may be related to the functional activity of such cells Cells of this type were not found in the biopsy specimen taken from our patient, which was, however, taken from the peripheral part of the ovary

Turner's syndrome is usually regarded as due to a failure of the primitive indifferent gonad to develop at all, possibly because of failure of the germ cells to migrate into it, or because of some as yet unknown environmental factor (Polani et al 1954, Grumbach et al 1955, Lennox 1956, Segal and Nelson 1957) The failure of gonadal differentiation leads to the development of a " neuter " state which, in mammals, appears to be morphologically more closely linked to the female form than to the male This is confirmed by the well-known female form of the eunuch and by the classical observation of Jost (1953) that rabbits castrated early in intrauterine life develop into morphologically female adults

Gonadal Agenesis

It is impossible to reconcile the histological appearance of the ovary in the present case with any theory of gonadal agenesis The gonad, far from remaining as a primitive indifferent genital ridge, has developed into an organ which is an apparently normal infantile ovary containing germ cells Wilkins (1957) includes in his discussion of Turner's syndrome a group of cases in which a small amount of ovarian germinal tissue is present and to which he gives the name gonadal hypoplasia Kerkhof and Stolte (1956) described 2 of these cases in adult women, both of whom complained of primary amenorrhœa and were of female habitus with hair growth of female distribution and normal urinary excretion of gonadotrophic hormones A small biopsy specimen from each ovary showed the typical appearances of gonadal agenesis in one woman, and in the other woman solitary primordial follicles were seen in both ovaries and there were two follicular cysts, the remainder of the tissue consisting of ovarian stroma Since the 2 patients were clinically similar it was assumed that germ cells had been missed in the biopsy specimen from the first case In both these cases, however, the nuclear sex was female A similar case was described by Hoffenberg et al (1957, case 2), whose patient was exceptional in that she had

had irregular menstruation between the ages of 15 and 21 Sections of her ovaries showed many primordial follicles The nuclear sex was not determined, but the polymorphonuclear leucocytes were of female type In these cases the concept of hypogonadism is tenable, but in the present case this hypothesis will not explain the apparent reversal of the genetic sex

A case which more nearly resembles the present one in the histological appearances of the ovary was described by Atria et al (1948) It was clinically typical of Turner's syndrome in that the patient was stunted, had webbing of her neck, cubitus valgus, and underdeveloped breasts and pubic hair, and had never menstruated The level of follicle-stimulating hormone in the urine was raised At necropsy, at the age of 20, infantile internal genitalia were found the hypoplastic ovaries each weighed about 2 5 g and contained many primordial follicles with oogonia The nuclear sex is not stated If it was male, the concept of Turner's syndrome as a manifestation of intrauterine gonadal failure would have to be reconsidered

Klinefelter's Syndrome

The condition of our patient may be regarded as an analogue or mirror image of Klinefelter's syndrome with female nuclear sex (Klinefelter et al 1942), in which all grades of testicular development, from a simple mass of Leydig cells to a complex tubular system showing spermatogenesis, may be found (Bunge and Bradbury 1956, Segal and Nelson 1957) These two conditions—Klinefelter's syndrome with female nuclear sex, and the syndrome exhibited by the present patient—are instances of complete sex reversal, the genetic sex revealed by examination of the cell nuclei and the phenotypic sex revealed by the bodily habitus and the histological appearance of the gonad being diametrically opposed

A theory which offers an explanation of this discrepancy has been published by Hoffenberg and Jackson (1957), who postulate the presence of an evocator (itself normally determined by the genetic constitution of the individual), which determines the direction of differentiation of the primitive gonad and thence of the development of the wolffian or mullerian-duct systems They suggest that, in Klinefelter's syndrome, the male evocator is in the ascendant, and that the gonad is thereby stimulated to develop in the direction of a testis Such a theory, in reverse, would explain the findings in the present case, and, with the extension that the full effect of a female evocator may not be apparent on the cells of an individual who is genetically male, would explain the embryogenesis of the commoner cases of Turner's syndrome with gonadal agenesis

True Hermaphroditism

A further possibility which must be mentioned is that the child is a true hermaphrodite having both testes and ovaries or ovotestes This could not be definitely excluded without serial sections of the whole of both gonads, but we think it extremely unlikely in view of the normal appearance of the ovaries, the perfect development of the mullerian-duct system, and the absence of any identifiable ectopic testicular tissue or wolffian structures

It will be interesting to see whether this child attains a normal stature and has a normal puberty Surgical reconstruction of the external genitalia will be carried out later At present her ovaries are histologically normal for her age, but it is possible that the cells, being of male genetic sex, will be unresponsive to the pituitary hormonal stimulus of puberty Perhaps such unresponsiveness would explain the condition of the patient described by Atria et al (1948), although in the absence of knowledge of the nuclear sex this is only speculation Against such an explanation must be set the fact that one of the patients of Hoffenberg et al (1957) menstruated despite agenesis of the gonads, as did 2 patients of Polani (1957) with male nuclear sex, in whom, however, laparotomy was not performed

Summary

A case of anomalous sexual development is described in which the bodily habitus and sexual organs were of female morphology except for enlargement of the clitoris, and the ovaries appeared histologically normal for the age of the patient, but the nuclear sex was male

The concept of Turner's syndrome is reviewed, and it is concluded that the embryogenesis in the present case can best be explained as due to the ascendancy of an abnormal female evocator acting on the indifferent gonad in the earliest days of intrauterine life, and that failure of development of the gonad may not explain the ætiology of this syndrome

ADDENDUM

Since this paper was submitted for publication similar cases have been recorded by Prof R B Greenblatt at the 1957 Laurentian Hormone Conference, and by Hoffenberg and Jackson (case 20) (*Brit med J* 1957 ii, 1457)

We wish to thank Dr R H White-Jones, who referred the case, and Miss I Forshall, F R C S, under whose care the baby was admitted to hospital, for permission to publish, and Dr E G Hall for criticising the manuscript A summary of this case-report was read at the symposium on Nuclear Sexing held at King's College Hospital, London, on Sept 6, 1957

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INTRATHECAL PHENOL FOR INTRACTABLE PAIN*

SAFETY AND DANGERS OF THE METHOD

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AT the back of the minds of those who treat patients with intractable pain, there is always the hope that a substance may be found which will destroy the nerve-fibres conducting impulses subserving the sensation of pain, while leaving intact all other fibres With such a substance, a selective chemical posterior rhizotomy might be carried out by intrathecal injection It was, then, with much interest that we heard that Maher was treating the severe pain of cancer by the intrathecal injection of substances thought to unite with nervous tissue

In 1955 Maher published his first results of treating pain in cancer by the intrathecal injection of phenol in glycerin and of silver nitrate in water and glycerin; in 1957 he reported further results, using phenol dissolved in glycerin and ethyl iodophenylundecylate (‘Myodil’), and silver nitrate in a solution of phenol in glycerin.

These solutions were injected with the patient lying in such a position as to allow the solutions, which are heavier than cerebrospinal fluid (C.S.F.), to flow into the arachnoid sac surrounding the selected nerve-roots. When given in this manner, the full concentration of the solution falls on about two roots, with little or no effect on neighbouring roots. Maher noted that the substances affected the function of the nerve-roots within a few minutes and that the maximal effect passes off within 10 to 15 minutes. The patient, after lying in the required position for a quarter of an hour, can then move into a sitting position, without any further manifestations of the action of the substances on the nerve-roots.

Anyone hearing of this method of dealing with intractable pain will want to know if it is effective and if it is free from danger. We report here an investigation of the toxicity of phenol in myodil and of silver nitrate in phenol and glycerin, injected intrathecally in quantities of 1 ml. or less. We are not reporting our results obtained in relieving pain—suffice it to say that we have obtained relief in about a half of the cases—nor are we now reporting our investigation of the mode of action of phenol on nerve fibres. Although we have so far had the opportunity of testing Maher's method in only a few cases, our limited experience may be useful to others who have the problem of helping patients with intractable pain.

Undesired side-effects are seen with most methods used in the treatment of the chronic pain of cancer. Analgesic drugs often cause nausea, light-headedness, and drowsiness; anterolateral cordotomy has complications such as disturbed bladder control; and leucotomy may give rise to defects of judgment, initiative, and intellectual capacity. Intrathecal injections might result in a reactive meningitis or arachnoiditis, in paraplegia, or in damage to nerve-fibres which should be preserved. Changes in C.S.F. cell and protein contents have been looked for as a possible indication of damage to and reaction of the surrounding tissues, and in particular of the meninges. The rate of diffusion of phenol out of myodil into the C.S.F. has been studied, for it is likely that the toxic effects of phenol occur when its concentration in the C.S.F. rises above a certain level.

In all but a few cases reported here the phenol in myodil has been a 7.5% solution; in the remainder it has been a 5% solution. We report only the results of injecting the stronger solution, for if such a solution may be used with impunity, then the weaker solution is likely to be innocuous. The 7.5% solution of phenol in myodil was given in amounts of 0.75, 1.0, or 1.5 ml. The silver nitrate could not be given in watery solution, for then some of the phenol would be present in watery solution, and it is essential that the phenol should remain in solution in a lipid. Accordingly the silver nitrate was dissolved in as small a quantity of water as possible, and this small quantity of solution was added to a 5% solution of phenol in glycerin; 0.75 ml. of this solution was injected. These solutions were injected intrathecally caudal to the 12th thoracic vertebra in all cases, except in three, in which the injections were made immediately caudal or cranial to the 7th cervical vertebra.

Observations

Evidence of Undesired Side-effects

Phenol in myodil.—Thirty injections of phenol in myodil have been given.

In no case has any weakness of the musculature followed the injection, even when invasion of the peripheral nerves by cancerous tissue had already caused some weakness. After one of the injections, the patient had retention of urine and such diminution in anal sensation that he did not know when fæces were being passed; this patient had had a very slight disorder of defæcation before the injection, due to infiltration of the pudendal nerves by a cancer originating in the rectum. Following the other twenty-nine injections, micturition and defæcation were unaffected.

Silver nitrate in phenol in glycerin has been injected in thirteen cases.

There was a slight increase in weakness of an already affected limb in six, an increase in an already disturbed control of micturition in two cases, and an increase in an already disturbed control of defæcation in one. In one patient, who had a carcinoma of the breast with metastases, anæmia, and diabetes mellitus, the injection was followed by a severe meningeal reaction. 2 days after the injection the patient died. Since this experience no further injections with silver nitrate have been carried out.

Necropsy Evidence of Toxicity

Phenol in myodil.—As seven of the patients who had this injection have eventually died from cancer, it has been possible to determine changes brought about by the injection. In none was there any macroscopic abnormality which could be attributed to the injection.

There was no fibrosis outside or inside the spinal theca; the meninges were not thickened and the pia mater and arachnoid membrane were of normal appearance. The nerve-roots appeared normal, in so far as they were not involved by the cancerous tissue; they were neither bound down by adhesions nor thickened nor shrivelled.

The histological investigation of the nerve-roots from these cases and from cats treated in the same way is being undertaken by Dr. Marion Smith; the results of this investigation will be reported later.

Silver nitrate in phenol in glycerin.—Five of the seven patients mentioned in the previous paragraph, showing no gross abnormality attributable to the injections, had also had injections of the silver nitrate solution.

However, as has been said already, in one patient a marked meningeal reaction developed after an intrathecal injection given in the lower cervical region. In this case leptomeningitis was found at necropsy; this was most intense caudal to the 8th cervical vertebra, where the injection had been given. The reaction involved the whole of the pial sac. It was greatest in the lower thoracic region and more evident posteriorly than anteriorly. This distribution was probably due to the position—half sitting up—in which the patient had been nursed after the injection.

Evidence of Toxicity as Judged by Changes in Cerebrospinal-fluid Constituents

Phenol in myodil.—In nine patients specimens of C.S.F. were taken and examined after the intrathecal injection (table I).

In eight patients the cells were counted and the protein estimated both before and after the injection; in one, no specimen was taken before the injection. The specimens were taken at various intervals after the injection. There were few consistent changes. In one patient there was definite slight polymorphonuclear leucocytosis in the fluid 24 hours after the first injection, but it did not recur 24 hours after a second injection. In these nine patients the maximal effects were a polymorphonuclear leucocytosis of 73 per c.mm. 24 hours after an injection, and an increase in protein content from 90 mg. per 100 ml. to 140 mg. in 5 days, and the minimal

TABLE I—CHANGES IN C S F. CONSTITUENTS FOLLOWING INJECTION OF 7½% PHENOL IN MYODIL 0 75–1 0 ML.

Patient no	Before injection			After injection														
				¼–½ hr			1 hr			6–24 hr			24–36 hr			2–8 days		
	P	L	Prot	P	L	Prot	P	L	Prot	P	L	Prot	P	L	Prot	P	L	Prot.
1 1st injection	0	0	30										73	1	75			
2nd injection	73	1	75							25	3	40						
2	0	1	35	0	0	35				4	3	60						
3	0	1	35	0	1	35	0	1	45									
4 1st injection	0	2	90	0	1	90										2	9	100
2nd injection				2	10	110				2	11	110	1	8	110			
5 1st injection	0	1	35	0	0	50										0	1	30
2nd injection	0	1	30	0	1	30												
6	0	7	90													0	5	140
7	0	0	80													0	1	90
8																0	12	40
9	0	4	90	0	0	90										0	0	95

P—Polymorphonuclear leucocytes (per c mm), L—Lymphocytes (per c mm), Prot —Protein (mg per 100 ml)

effects were no change in the cell count and an increase in protein from 90 mg to 95 mg per 100 ml in 5 days These changes, however, may be regarded as very slight

Silver nitrate in phenol in glycerin—In very few patients was the C S F examined after the injection of silver nitrate 0 81 mg (gr $^1/_{80}$) dissolved in water and added to a solution of phenol in glycerin) The findings in these specimens are given in table II Apart from the death from chemical meningitis, the results do not suggest that this form of injection is very toxic

Rate of Diffusion of Phenol out of Myodil into C S F

Phenol acts on tissues differently according to whether the solvent is water or a lipid As the phenol injected into the C S F in myodil or glycerin is immediately surrounded by an aqueous fluid, it is important to know its rate of diffusion into the C S F It is evident that the amount diffusing into the C S F produces no marked reaction; for the changes in the cellular and protein constituents of the fluid are slight

In the first instance observations were made on the diffusion of phenol into C S F in vitro Later, the diffusion in patients was determined by taking specimens at intervals after the intrathecal injection

The *method of estimating phenol* was similar in the in-vitro and in-vivo experiments For the estimation in the in-vivo experiments, 1 ml of C S F was added to 4 5 ml of Folin and Ciocalteau's reagent diluted 1 3 with water The precipitated proteins were centrifuged, and to 5 ml of the supernatant fluid was added 2 5 ml of 20% sodium carbonate solution (w/v) The tube was placed for 5 minutes in a waterbath at 37°C to bring up the blue colour, this was compared with that of a standard solution containing 0 1 mg of phenol, which had been treated similarly In the in-vitro experiments it was found that the C S F contained so much phenol that it was necessary to dilute it with distilled water before the estimation of the phenol The amount of dilution necessary to give a satisfactory final colour was found by trial and error As a result of this dilution, it was found unnecessary to centrifuge the specimen after the addition of dilute Folin and Ciocalteau's reagent, for the protein had been " diluted out " Generally, a 1 in 10 dilution was found to be most satisfactory 1 ml of this was added to 3 ml of water in a test-tube, followed by 3 ml of dilute Folin and Ciocalteau's reagent and then by 2 5 ml of the sodium carbonate solution A standard was prepared in the same way, using 0 1 mg of phenol in 1 ml, and the colours developed were compared

TABLE II—CHANGES IN C S F CONSTITUENTS FOLLOWING INJECTION OF 5% PHENOL IN MYODIL 0 75 ML CONTAINING 0 81 MG OF SILVER NITRATE PER ML

Patient no	Before injection			After injection											
				½–1 hr			24–48 hr			1 week			1–2 weeks		
	P	L	Prot.	P	L	Prot	P	L	Prot.	P	L	Prot	P	L	Prot.
5	0	0	40										0	1	180
7	0	1	90							2	2	220	1	3	120
8	0	0	90							0	3	105			
9	0	0	95	0	0	110									
10							3000	100	1800						

Procedure of in-vitro experiments—25 ml of normal C S F was layered carefully on top of 3 ml of 10% phenol in myodil in a 50-ml measuring cylinder To prevent turbulent mixing of the two liquids, the C S F was delivered upwards by means of a pipette, the end of which had been made J-shaped The fluid was covered with a layer of liquid paraffin to avoid evaporation of phenol The measuring cylinder was then incubated at 37°C for 22 hours

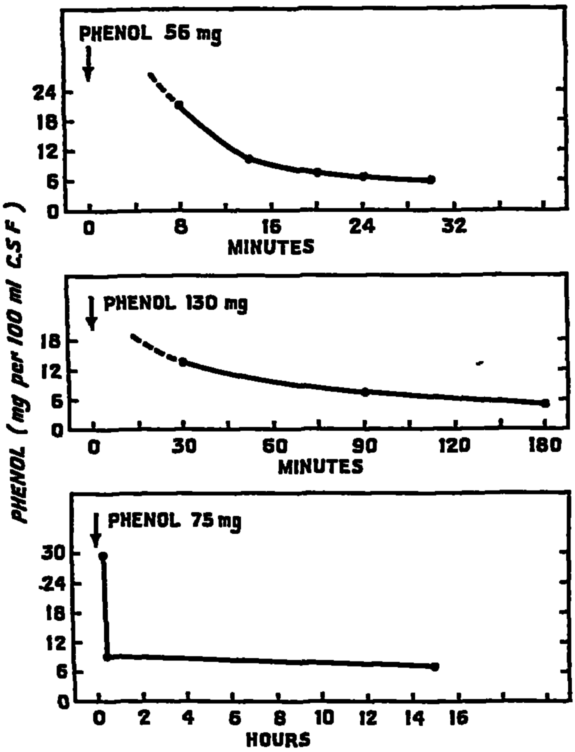
At intervals of ½, 1½, 3½, 6½, and 22 hours, 1 ml of C S F was slowly removed from the centre of the column, and its phenol content was estimated The concentration of the phenol at the centre of the fluid column was taken as representative of that of the whole column, on the assumption that the phenol diffusion gradient was linear

TABLE III—RATE OF DIFFUSION OF PHENOL FROM MYODIL INTO C S F IN VITRO

Times from start of experiment at which specimens were taken (hr)	Percentage of phenol transferred from myodil into C S F
½	4 0
1½	9 3
3½	14 7
6½	25 5
22	32 1

Results of in-vitro experiments—The results of a typical experiment are presented in table III In the actual experiment reported, the surface area of the liquid interface in the graduated cylinder was 6 2 sq cm , the calculated rate of diffusion was 4 5 mg per sq cm in the first 1½ hours At first there was a rapid diffusion of phenol out of the myodil , as the concentration in the supernatant C S F rose, the diffusion took place more slowly

Procedure of in-vivo experiments—In fourteen patients, the local concentration of phenol in the C S F was estimated It was assumed that there was no phenol in the C S F before the injection , the amount of phenol in body fluid is known not to exceed about 0 5 mg per 100 ml —an amount considered insignificant in relation to that injected The specimens of C S F were taken either through the needle by which the injection had been made (but only after C S F had been allowed to flow through the needle to wash out all traces of the myodil solution) or through another needle one vertebral space caudally When the fluid was withdrawn at intervals up to 35 minutes after the injection, the patient was not moved from



Graphs to illustrate the rate of diffusion of phenol out of myodil into the local C.S F in 3 of the patients

the lateral position When the fluid was withdrawn at intervals of hours or days after the injection, the patient was allowed to move about normally

For the first 24 hours after an injection, however, the patient was kept in a sitting or semi-sitting position, to prevent the phenol in myodil from flowing rostrally into the cranial cavity After that time he was allowed up and no restrictions were placed on his walking about The specimens of fluid then taken were local to the site of the injection When a patient lies in the lateral position, myodil, being heavier than C S F, spreads locally for about the depth of a vertebra in each direction from the point of the injection After the patient has been sitting or standing, the myodil collects at the bottom of the thecal sac, as shown by X-ray examination, in this case the myodil is caudal to the point of the needle through which the sample is being taken

Results of in-vivo experiments—The rates of diffusion of the phenol out of myodil into the local C S F are shown graphically in the figure, each curve gives the findings in a different patient All other results were similar to these examples It is apparent from the figure that the phenol content of the C S F in the immediate neighbourhood of the injection was relatively high soon after the injection, it fell considerably within the 1st hour, after the 1st hour, and during the subsequent days, the fall was only very slight In every case the initial phenol content of the C S F was always the highest

Although in the in-vitro experiments the amount of phenol transferred to the C S F continued to rise during the first 24 hours after the injection, such diffusion was not found in the in-vivo experiments There may be several reasons for this The phenol is taken up by nervous and other tissue, the C S F surrounding the phenol in myodil is constantly flowing, so that fluid with a relatively high phenol content is removed or diluted by uncontaminated C.S.F It is seen radiologically that the myodil containing phenol breaks up into droplets to some extent, thereby increasing the interface between the myodil and the C S F and permitting more rapid diffusion And it is possible that phenol may be removed from the C S F into the vascular bed

The effects of phenol on nervous conduction are manifest $1^1/_2$ to 2 minutes after the injection, rising to their maximum within $^1/_2$ minute, and tending to pass off in 10 minutes From the physiological effect it would appear that the amount of phenol leaving the myodil, and eventually being fixed in the nervous tissue, must be great within the first 5 minutes This rapid transfer is not apparent in the figure, the fall alone is shown on the graphs We do not know what content of phenol in watery solution is needed to block nerve-fibres The reason why the patient can be moved within 15 minutes of the injection is probably that the concentration of phenol in watery solution is then too small to affect the nerve fibres, by that time the phenol has been taken up by the nervous and other tissues, and an appreciable quantity has passed into the C S F In some cases no therapeutic effect, and even no local anæsthetic effect, was obtained It is apparent from the manner in which the phenol leaves the myodil that if there is no effect within the first few minutes, there will be none subsequently, and that in fact is what has always been found

Discussion

In view of our experience, intrathecal injection of silver nitrate in phenol and glycerin seems to be dangerous, when performed in the cervical region The intrathecal injection of phenol in myodil in the concentration used is safe, and we consider that this method is worthy of trial before surgical division of sensory pathways is undertaken

It is 90 years since Lister introduced phenol as an antiseptic into medicine Experience has shown that phenol is toxic, and so it comes as a surprise to hear that it can be injected intrathecally in fairly strong solution

The effect of phenol on tissues and organisms varies according to the solvent used In watery solution phenol is penetrating and sclerosing, it is well known to all practising doctors that phenol in glycerin, appropriately used, is harmless Equal quantities of pure phenol and pure camphor have been used in the treatment of tinea In this form, phenol is still antiseptic and analgesic, but it is far less caustic However, observations of the effect of phenol on the skin have little bearing on the possible effects of phenol within the thecal sac, surrounded by C S F and in contact with nervous tissue

To the best of our knowledge, toxic effects have been seen only when the phenol was used in watery solution Evidence of damage to the nervous system is scanty

Greenfield et al (1955) concluded that phenol, "if introduced in considerable concentration (0 5%) would be expected to lead to immediate lesions of the roots of the cauda equina with a corresponding symptomatology", this refers only to phenol in watery solution (Greenfield, personal communication, 1956)

Weston Hurst (1955) reported the results of an investigation in monkeys of certain substances which might be expected, when introduced intrathecally, to cause damage to the nervous system from arachnoiditis, one monkey which received intrathecally phenol (as a watery 2% solution) died after 13 days with greatly dilated ventricles. On the other hand large amounts of a dilute watery solution of phenol have been administered intrathecally to humans without causing death. Suvansa (1931) reported that he had treated tetanus by giving intrathecally 0.25% solutions of phenol in water in doses of 30–40 ml. to adults and 12–20 ml. to children. This treatment brought the patients successfully through the period of hyperexcitability of the central nervous system, but caused nephritis.

A legal case was brought in 1953 against the Ministry of Health and Messrs. Ciba. It was claimed that the small amount of a 5% solution of phenol in water that might have leaked through a hypothetical and invisible crack in an ampoule of cinchocaine (' Nupercaine ') was sufficient to cause severe arachnoiditis and consequent paraplegia; and this claim was regarded as established. It is well known to neurologists that severe meningeal reactions causing paraplegia sometimes follow spinal anæsthesia; such cases have been reported by Zeckel and Behr (1933), Kennedy et al. (1945), Kennedy et al. (1950), Macken and Martin (1950), and Greenfield et al. (1955).

Although we have emphasised that, with this method of treating intractable pain, the phenol is in lipid solution, we have shown that the phenol diffuses into the C.S.F., resulting in the presence of a watery solution of phenol within the spinal canal. However, with the amounts and concentrations used so far—recently up to 1 ml. of an 8% solution or 3 ml. of a 7.5% solution—undesired pathological effects have not followed. More severe meningeal reactions often follow air encephalography, which is a well-established diagnostic procedure. We conclude that the injection of phenol in myodil for the relief of pain, especially the pain of cancer, appears to be justified.

Summary

An investigation is reported of the toxic effects of phenol in ' Myodil ' and of silver nitrate dissolved in phenol in glycerin, injected intrathecally as a treatment for intractable pain.

The toxic effects are considered under the categories of undesired clinical effects, evidence of toxic effects found post mortem, and changes in the cerebrospinal fluid.

As phenol is relatively non-toxic in lipid solution and relatively toxic in watery solution, the rate of diffusion was investigated of phenol out of lipid solution into the C.S.F.

It is concluded that at least 1 ml. of a 7.5% solution of phenol in myodil can safely be injected intrathecally. The solution of silver nitrate in phenol in glycerin is less safe than the phenol in myodil.

We should like to thank Dr. E. A. Carmichael and Dr. J. N. Cumings, who provided us with opportunities and encouragement to carry out this investigation, and the physicians and surgeons at the National Hospital and Mr. I. R. McCaul of the Whittington Hospital, who so kindly referred patients to one of us (P. W. N.).

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INTRAGLOSSAL INJECTIONS IN UNCONSCIOUS PATIENTS

AN ALTERNATIVE TO INTRAVENOUS INJECTION

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IN the treatment of unconscious or anæsthetised patients it is very often desired to inject stimulants, antidotes, &c., intravenously to ensure rapid onset of action. In the obese and in the collapsed adult and in young children it may be impossible to find a vein. Since intramuscular injections may take ten minutes or more to take effect, another method, with a rapid onset of action, is an advantage. Such a method is injection into any highly vascular organ. For instance, it has been common practice for many years to inject oxytocic drugs into the uterus after cæsarean section (and injections into the liver during abdominal surgery have been described). The tongue is a highly vascular and easily accessible organ. Drugs injected into the tongue start to take effect in 40–80 sec.—e.g., the tachycardia after atropine—as against 15–30 sec. after intravenous injection.

Technique

Although the injection can be made into any part of the tongue, I now insert the needle via the ventral surface because bleeding on withdrawal of the needle is less common there. The two veins on either side of the midline should be avoided. With the patient lying supine the tip of his tongue is picked up in a gauze swab between the index finger and thumb of the left hand and drawn out of the patient's mouth. The syringe is held in the right hand, and the needle is inserted directly posteriorly (vertically downwards). Volumes of up to 2 ml. may be injected. Provided a sharp needle, size 16–18, is used, bleeding is uncommon on withdrawal of the needle. Anæsthetists may prefer to lift the tongue forward with a pair of Magill's forceps, or any other pair of blunt forceps will do. In anæsthetised patients the needle may be left in situ for serial injections of analgesics, &c.

Indications

Emergencies.—In the treatment of any unconscious, comatose, or collapsed patient, whether from injury, disease, or drugs, where a rapid onset of action is necessary, this method can be used with advantage.

In anæsthetic practice.—The intraglossal route may be used for most of the drugs used—relaxants and their antagonists, analgesics and their antagonists, hypotensive drugs and vasopressors, procaine derivatives and so on. Irritating solutions mentioned below should be avoided.

Special mention should be made of suxamethonium (' Scoline,' ' Brevidil,' ' Anectine '). I give this drug intraglossally in double the dosage I would have used intravenously —e.g., 100 mg. for an adult. Paralysis usually develops 90 sec. later, depending on the vascular condition of the patient, being most rapid in healthy children, when it may start in 45 sec. Muscular fibrillations are usually absent or minimal. The effect wears off more gradually but in much the same time as after intravenous injection. A flush around the face and neck may sometimes follow for a short time.

Contraindications

Any solution known to be irritating should be avoided, except perhaps as a life-saving measure. Barbiturates should not be used, nor should solutions of tubocurarine and of phenothiazine derivatives, because a tender lump as big as a pea is left for a week or so. Dimethyltubocurarine iodide, being in aqueous solution, can be used as an alternative to tubocurarine, and gallamine can be used. Pethidine, nalorphine, atropine, and neostigmine can all be used.

Conclusion

The practice of injecting into the tongue may at first seem unæsthetic but it can be extremely useful when veins are inaccessible As an anæsthetist I have been using it for five years without mishap, and recommend it to general practitioners and anæsthetists alike As a general guide it may be safely said that any solution which can be injected hypodermically without irritation can safely be injected into the tongue It should not be practised in conscious patients, because it is rather painful

Summary

When veins are inaccessible, and a rapid onset of action is required, drugs may be injected into the tongue in unconscious patients The onset of action takes 45–90 seconds

Intraglossal injection is recommended for stimulants, antidotes, &c , in emergencies and in clinical anæsthesia Particular mention is made of the relaxant suxamethonium Irritant solutions should not ordinarily be used

PHÆOCHROMOCYTOMA OF THE URINARY BLADDER

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THIS is an account of a phæochromocytoma arising in the wall of the urinary bladder Similar cases have been recorded only twice (Zimmerman et al 1953, Pugh 1956) The tumour produced pressor amines and gave rise to a striking clinical picture which should be easily recognised if met again The scanty literature gives a false impression of the rarity of the tumour, we hope later to report several examples collected from British hospitals

Case-report

The patient is a married woman, aged 48 At the age of 13 she began to have curious attacks after micturition As soon as the bladder was emptied, she experienced forcible " thumping " of the heart, a throbbing " bursting " headache, intense pallor of face and hands, coldness of the fingers and usually sweating These attacks, which lasted for only a few minutes, took place only in summer, and they ceased with the menarche, at 15 But they reappeared in 1950, when she was 41, and were again confined to the summer months, occurring about five times a week They became more frequent and more severe until, in 1953, they followed every act of micturition and lasted about an hour and a half

She was admitted to a nursing-home in October, 1953, for observation but had no attacks She was admitted to hospital in January, 1954, for investigation Her blood-pressure varied from 160 100 to 230 110 mm Hg, and her basal metabolic rate (B M R) was +33% Intravenous phentolamine hydrochloride (Rogitine ') 5 mg produced a fall of blood-pressure from 190 100 to 170 85 mm Hg in one minute, this result was considered equivocal Renal-function tests and an intravenous pyelogram were normal, as were the electrocardiogram and chest radiograph A diagnosis of paroxysmal tachycardia, occurring in a patient with hypertension and mild thyrotoxicosis, was thought likely She was given 100 mg of methyl thiouracil daily together with phenobarbitone gr ½, t d s , discharged from hospital, and observed as an outpatient

Attacks occurred in the summer of 1954 but seemed to be less frequent and lasted only a few minutes Blood pressure readings varied from 190/100 to 220/110 mm Hg Treatment with methyl thiouracil and phenobarbitone was continued, and occasional mild attacks occurred in the summer of 1955, the blood-pressure remained about 200/100 Methyl thiouracil medication was reduced to 50 mg daily in March, 1956, and withdrawn altogether four months later, phenobarbitone was continued Although during 1956 blood-pressure readings were rather higher—250/110–270/150—the symptoms disappeared entirely from April onwards There was no radiological or electrocardiographic evidence of cardiac hypertrophy, the ocular fundi showed variation in arterial calibre, with venous nipping but no hæmorrhages or exudates and no papillœdema The patient was leading a busy life, which included a large daily newspaper round in a country district

In July, 1951, a sample of urine was tested for pressor amines at University College Hospital, London, by the cat blood-pressure method (Moulton and Willoughby 1955) It was found to contain 0 8 mg of noradrenaline per ml , indicating the presence of a phæochromocytoma Intravenous pyelography was repeated in an attempt to locate the neoplasm there was no displacement of the kidneys, and the renal pelves and ureters were normal, an indentation in the vault of the bladder was attributed to pressure from uterus or distended bowel Tomograms of the renal areas were normal No further investigations were made, and she continued to attend as an outpatient, remaining free from symptoms until January, 1957, when a bout of hæmaturia, lasting ten days, led to readmission and cystoscopy

A smooth tumour, with a broad base, was seen in the posterior bladder wall above the trigone It was considered likely to be the phæochromocytoma, and the decision was made to remove it, controlling the blood-pressure with phentolamine and noradrenaline (Helps et al 1955)

Laparotomy was done on Feb 26, 1957, and the tumour excised from the posterior bladder wall without difficulty Both adrenals were normal, and no other neoplasm was found in the abdomen The blood-pressure, measured every half to two minutes throughout the operation, varied from 120/80 to 270/170 mm Hg (fig 1) Phentolamine was given intravenously in doses of 5 mg up to a total of 15 mg On ligation of the last vein draining the tumour the blood-pressure fell to 100/80, and an intravenous infusion of noradrenaline was started, it was adjusted to maintain the blood-pressure at about 170/110 for the remainder of the operation The infusion was stopped three hours later, and the blood-pressure remained at about 115/75 mm Hg for the next twelve hours Next day it was 140/90 and it remained at, or near, this level until the patient was discharged from hospital five weeks later Her urine, examined during convalescence, contained 0 01 mg of noradrenaline per ml The B.M.R was +6%

She was seen several times as an outpatient in the next six months She remains free from symptoms and looks very well Her blood-pressure varies from 190/100 to 210/105 mm Hg and her ocular fundi show variation in arterial calibre as the only abnormality When last seen she remarked that she could never have got through the recent hot weather without her operation

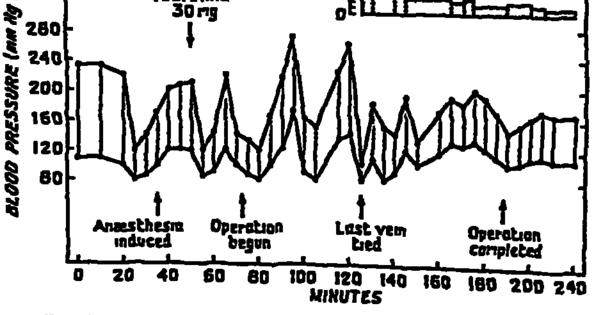

Fig 1—Blood-pressure during operation for removal of phæochromocytoma

Fig 2—Operation specimen showing a cluster of nodules on one aspect of the tumour (Actual size)

PATHOLOGY

The specimen was a roughly ovoid brown-red mass measuring 13 × 8 × 8 cm and weighing 74 g The greater part of the surface was smooth and shining, apart from a small gelatinous translucent area 2 cm in diameter A cluster of small nodules (up to 1 cm in diameter) projected from the mucosal surface (fig 2) The cut surface of the specimen showed yellow and red patches, it turned deep brown after a few hours' immersion in 10% formol saline solution The fixative became brown after a few days—a characteristic feature of phæochromocytoma

An unfixed piece of the tumour examined for pressor amines contained 2 3 mg of adrenaline and noradrenaline per gramme

Histological examination revealed trabeculæ and solid acini consisting of polygonal cells The cells contained delicate cytoplasmic granules and showed occasional nuclear pleomorphism Capillaries were abundant throughout the tumour The chromaffin reaction was not obtained Histochemical examination of the tumour cells showed lipid and protein in the cytoplasmic granules

The tumour lay outside the muscle coat of the bladder but was not clearly demarcated from it A few small islands of tumour cells infiltrated between muscle bundles Arterioles showed conspicuous intimal fibrous thickening

The close relationship of tumour cells to abundant capillaries *provided the main clue to its endocrine origin* However, without the results of biochemical investigations it is doubtful whether the neoplasm could have been recognised as a phæochromocytoma

Discussion

The clinical history and demonstration of pressor substances in the urine and in the tumour leave little doubt that the attacks both in childhood and middle life were due to squeezing of the growth by contraction of the bladder muscles Quiescence coincided with the menarche, but recrudescence cannot be related to the menopause, which has not yet arrived It seems unlikely that the tumour could have disappeared after the menarche and reappeared at the age of 41, and an alternative explanation is that it did not secrete pressor substances during the quiescent period Such intermittent activity is a characteristic feature of endocrine neoplasms

Any explanation of the restriction of symptoms to hot weather must be purely speculative

It is known that some phæochromocytomata produce mainly adrenaline and some mainly noradrenaline (Goldenberg et al 1954), and that infusion of noradrenaline causes a relatively symptomless hypertension (Barnett et al 1950) In the present case the persistently raised blood-pressure from 1953 onwards was probably associated with continuous secretion of noradrenaline We believe that superimposed secretion of adrenaline during warm weather would explain the paroxysmal attacks, a hypothesis which could be tested, in a future case, by differential estimation of the two substances in the urine by the method suggested by McMillan (1957)

The problem, then, is to account for production of adrenaline during the summer A possible clue is provided by Folkow and Von Euler (1954), *who showed that stimulation of certain* parts of the hypothalamus in the cat caused the suprarenal glands to secrete mainly adrenaline, whereas stimulation of other hypothalamic areas led to a secretion consisting mainly of noradrenaline It is not known whether human phæochromocytomata are subject to the same hypothalamic influences as the feline suprarenal medulla, but it is an interesting hypothesis If such hypothalamic control exists it could explain the postulated variation in secretion of pressor substances in the present case The intimate relationship of the temperature-regulating and sympathetic centres of the hypothalamus suggests that the activities of the one might influence those of the other Some such explanation might explain the restriction of this patient's attacks to warm weather

It is impossible to assess the significance of the apparently beneficial effect of methyl-thiouracil therapy The raised B M R in patients with phæochromocytoma is probably due to increased oxidation in the tissues, brought about by excess of catechol amines and not of thyroid hormone The normal B M R and normal urinary excretion of adrenaline and noradrenaline, after excision of the tumour, accord with this view

The blood-pressure remains moderately raised several months after removal of the tumour, a common finding in these cases (Peart 1954) The condition resembles essential hypertension, and its significance has been discussed by Goldenberg et al (1948) and Pickering (1955) This fixed hypertension was probably already present when the phentolamine test was made in 1954 and would explain the equivocal response

The structure of the tumour was not sufficiently characteristic to permit a diagnosis on histological grounds alone, and we regard its high adrenaline/noradrenaline content as much more convincing evidence of its nature The fickle chromaffin reaction is an unreliable *criterion*

Summary

A case is described in which a phæochromocytoma arose in the wall of the urinary bladder It produced pressor amines, which were detected in the urine and gave rise to characteristic paroxysmal attacks after micturition The attacks were confined to warm weather, the significance of this remarkable feature is discussed Since the histological features of such tumours are not always characteristic, the importance of estimating pressor amines in the tumour is emphasised

Our thanks are due to Dr Leslie Cole for permission to publish, to Mr J F R Withycombe, who performed the operation, to Dr *A M Barrett for his advice, and Dr N R Lawrie for the* biochemical estimations

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Preliminary Communication

A THEORY OF NERVE DEAFNESS

THREE types of impairment of hearing are generally distinguished

(1) *Conduction deafness* due to loss in the middle ear only, sensitivity for bone conduction being normal Often caused by thickening of the tympanum or by otosclerosis

(2) *Nerve deafness*, in which there is impairment of both air and bone conduction Associated with degeneration of the sensory cells of the organ of Corti in the inner ear or with other neural damage, such as a tumour of the eighth nerve

(3) *Central deafness*, which is rare and has no known peripheral origin, being regarded as a central disorder often associated with aphasia No further mention of this will be made here

There seems to be no mystery about conduction deafness, the auditory signal is simply attenuated, and this loss may usually be made good with a suitable external amplifier In nerve deafness, on the other hand, amplification does not make up for the loss, and the defect is not simple attenuation of the signal The condition has certain rather distinctive features

(1) There is some degree of confusion The older term "perception deafness", still sometimes used, indicates this clinical distinction

(2) The deterioration is mainly at the upper end of the frequency spectrum (presbyacusis), hearing for low frequencies often being normal

(3) The audiogram is generally "peaky", a sudden dip (loss of sensitivity) at about 4000 cycles being particularly common

(4) Tinnitus is common, but this may also occur in conduction deafness

(5) The curious phenomenon of loudness recruitment is common

Recruitment, which is almost certainly found only in nerve deafness, may be described as a shortening of the loudness scale

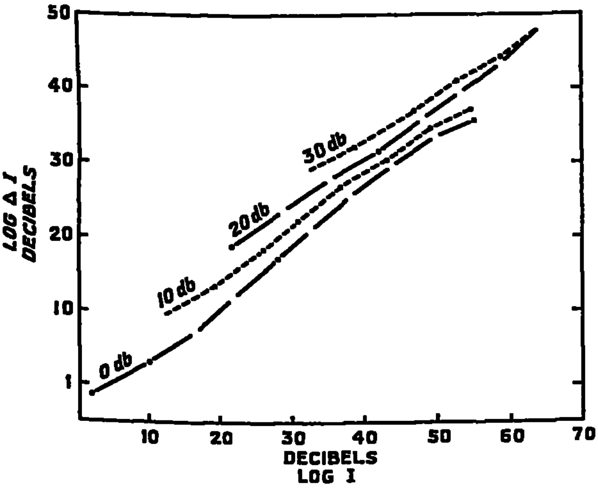

Fig 1—Effects of nerve deafness on differential threshold No additional masking has been added, tone pips are of same duration as above but following frequencies have been used 1000, 1500, 2000, 3000, and 4000 cycles per sec.

Each of 17 persons used was tested for absolute threshold at the above frequencies and compared with average ear to assess impairment for each frequency Subjects with the same absolute thresholds (i e, the same impairment) are grouped together This grouping is irrespective of frequency—subjects are combined for any frequency for which their absolute thresholds are equal Thus each subject may appear in several of the curves, at various frequencies Bone conduction to the mastoid process has been used throughout we are repeating the experiment for air conduction As in fig 1, slope flattens with increasing impairment It seems possible to estimate effective masking noise for various degrees of nerve deafness by comparing curves in figs 1 and 2 and selecting those giving best fit.

In cases of unilateral nerve deafness it may be demonstrated by applying the same tone to the two ears and asking the patient to balance the intensities for the two ears over a wide range of intensity Where there is recruitment, the deaf ear will require higher energies at the lower intensities, but, as the level rises, the difference in intensity for loudness balance decreases and may disappear In conduction deafness the ratio of the two energies will remain constant for loudness balance over the working range of hearing

Previous work on visual discrimination, where thresholds are supposed to be limited by the effective signal-to-noise ratio of the neural systems involved, suggests a possible explanation of nerve deafness We have regarded visual discrimination as limited by the channel capacity of the system, the channel capacity being a function of the number of fibres available for discrimination and the level of random neural activity, or "noise", tending to mask the signal Increase in the amount of noise should raise the threshold and tend to produce confusion Nerve deafness could be due to loss of channel capacity either through loss of functional fibres or through increased noise These two possibilities give rather different predictions

To test the hypothesis that nerve deafness is in some cases due to increased noise masking the auditory signals, we have compared the phenomena of nerve deafness with the effects of noise masking on normal hearing Their similarity is striking

Fletcher[1] found that, when he used thermal noise for masking pure tones, the high tones were primarily affected, in other words, he produced presbyacusis in the normal ear by masking with thermal noise It is well known that partial sectioning of the cochlear nerve produces presbyacusia in cats[2] and also in patients with Menière's disease[3] Thus it might be concluded that reduction in channel capacity decreases discrimination of high tones whether this reduction is the result of raised noise or of loss of functional fibres

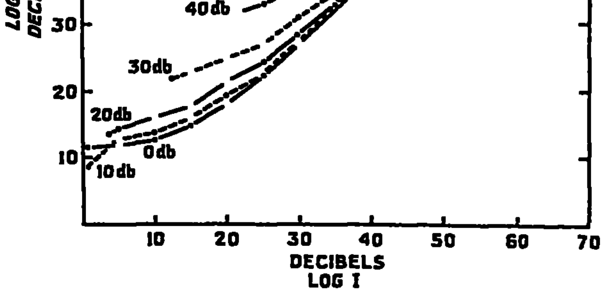

Fig 2—Effects of various levels of masking noise on threshold for detecting tone pip lasting 0 01 sec. against continuous tone Frequency of continuous tone and pip is 1000 cycles per sec Masking noise reduces slope Bone conduction was used. Pips slightly rounded to reduce transients

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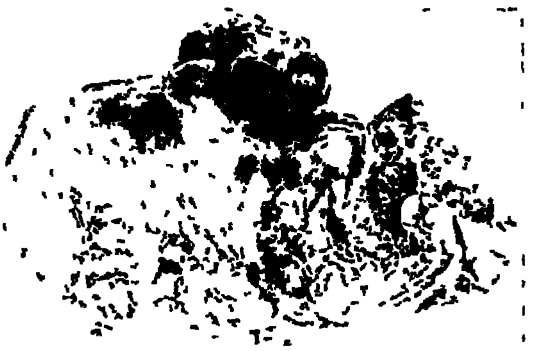

Fig 2—Operation specimen showing a cluster of nodules on one aspect of the tumour (Actual size)

PATHOLOGY

The specimen was a roughly ovoid brown-red mass measuring 13 × 8 × 8 cm and weighing 74 g The greater part of the surface was smooth and shining, apart from a small gelatinous translucent area 2 cm in diameter A cluster of small nodules (up to 1 cm in diameter) projected from the mucosal surface (fig 2) The cut surface of the specimen showed yellow and red patches, it turned deep brown after a few hours' immersion in 10% formol saline solution The *fixative became brown after a few days—a characteristic* feature of phæochromocytoma

An unfixed piece of the tumour examined for pressor amines contained 2 3 mg of adrenaline and noradrenaline per gramme

Histological examination revealed trabeculæ and solid acini consisting of polygonal cells The cells contained delicate cytoplasmic granules and showed occasional nuclear pleomorphism Capillaries were abundant throughout the tumour The chromaffin reaction was not obtained Histochemical examination of the tumour cells showed lipid and protein in the cytoplasmic granules

The tumour lay outside the muscle coat of the bladder but was not clearly demarcated from it A few small islands of tumour cells infiltrated between muscle bundles Arterioles showed conspicuous intimal fibrous thickening

The close relationship of tumour cells to abundant capillaries provided the main clue to its endocrine origin However, without the results of biochemical investigations it is doubtful whether the neoplasm could have been recognised as a phæochromocytoma

Discussion

The clinical history and demonstration of pressor substances in the urine and in the tumour leave little doubt that the attacks both in childhood and middle life were due to squeezing of the growth by contraction of the bladder muscles Quiescence coincided with the menarche, but recrudescence cannot be related to the menopause, which has not yet arrived It seems unlikely that the tumour could have disappeared after the menarche and reappeared at the age of 41, and an alternative explanation is that it did not secrete pressor substances during the quiescent period Such intermittent activity is a characteristic feature of endocrine neoplasms

Any explanation of the restriction of symptoms to hot weather must be purely speculative

It is known that some phæochromocytomata produce *mainly adrenaline and some mainly* noradrenaline (Goldenberg et al 1954), and that infusion of noradrenaline causes a relatively symptomless hypertension (Barnett et al 1950) In the present case the persistently raised blood-pressure from 1953 onwards was probably associated with continuous secretion of noradrenaline We believe that superimposed secretion of adrenaline during warm weather would explain the paroxysmal attacks, a hypothesis which could be tested, in a future case, by differential estimation of the two substances in the urine by the method suggested by McMillan (1957)

The problem, then, is to account for production of adrenaline during the summer A possible clue is provided by Folkow and Von Euler (1954), who showed that stimulation of certain parts of the hypothalamus in the cat caused the suprarenal glands to secrete mainly adrenaline, whereas stimulation of other hypothalamic areas led to a secretion consisting mainly of noradrenaline It is not known whether human phæochromocytomata are subject to the same hypothalamic influences as the feline suprarenal medulla, but it is an interesting hypothesis If such hypothalamic control exists it could explain the postulated variation in secretion of pressor substances in the present case The intimate relationship of the temperature-regulating and sympathetic centres of the hypothalamus suggests that the activities of the one might influence those of the other Some such explanation might explain the restriction of this patient's attacks to warm weather

It is impossible to assess the significance of the apparently beneficial effect of methyl-thiouracil therapy The raised B M R in patients with phæochromocytoma is probably due to increased oxidation in the tissues, brought about by excess of catechol amines and not of thyroid hormone The normal B M R and normal urinary excretion of adrenaline and noradrenaline, after excision *of the tumour, accord with this view*

The blood-pressure remains moderately raised several months after removal of the tumour, a common finding in these cases (Peart 1954) The condition resembles essential hypertension, and its significance has been discussed by Goldenberg et al (1948) and Pickering (1955) This fixed hypertension was probably already present *when the phentolamine test was made in 1954* and would explain the equivocal response

The structure of the tumour was not sufficiently characteristic to permit a diagnosis on histological grounds alone, and we regard its high adrenaline/noradrenaline content as much more convincing evidence of its nature The fickle chromaffin reaction is an unreliable criterion

Summary

A case is described in which a phæochromocytoma arose in the wall of the urinary bladder It produced pressor amines, which were detected in the urine and gave rise to characteristic paroxysmal attacks after micturition The attacks were confined to warm weather, the significance of this remarkable feature is discussed Since the histological features of such tumours are not *always characteristic, the importance of estimating* pressor amines in the tumour is emphasised

Our thanks are due to Dr Leslie Cole for permission to publish, to Mr J F R Withycombe, who performed the operation, to Dr A M Barrett *for his advice,* and Dr N R Lawrie for the biochemical estimations

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of the sheath, and for a mechanism which can be operated and rotated with one hand so that a finger of the free hand can be inserted per rectum to assist in the operation

Several rotatable machines have been designed on either side of the Atlantic, but in most of these the sheath has to be gripped to rotate it Accordingly the second hand is occupied, and the instrument no longer allows a free hand to examine the prostate per rectum

The resectoscope illustrated here (figs 1 and 2) is the result of attempts to fulfil the modern requirements in size, simplicity, and single-handed operating The telescope is the wide-field fore-oblique McCarthy type, which is interchangeable with all standard American patterns and gives a good clear view The grip is comfortable, and the distance between the first and second fingers has been reduced by dispensing with the lower guide-rail A light steady movement is assured by the addition of four small roller-bearings above and below the one remaining guide-rail A return spring is unnecessary because the movement is free, hence the dangerous rest position with the loop beyond the sheath, as occurs with the Baum-Rucker resectoscope, is avoided The natural movement of approximating the fingers and thumb while cutting is preferable to the Nesbit principle of cutting while extending the thumb

The sheath does not rotate on the moving parts, but the grip is equally comfortable with the instrument in the inverted position (fig 2) This enables the anterior half of the prostate and bladder neck to be resected as easily as the posterior half

Two sizes of sheath are provided 26 Charriere and 30 Charrière The smaller size is adequate for most work, the larger size enables a larger loop to be used if needed

This instrument has now been used in Bristol for the past eighteen months and has proved itself easy to operate, comfortable to handle, and simple to strip and clean Decreasing the complexity of the resectoscope has decreased the number of exasperating minor faults On several occasions more then 20 g has been resected in less than half an hour

The instrument can be supplied with duplicate telescopes, duplicate moving parts, panendoscope attachments, and two additional viewing telescopes (right-angled and retrograde) This set is completely self-contained with its own spare parts, which gives the urologist a considerable sense of security

I wish to thank Mr S T H Smith and Mr F T D Lowrie and the staff of the Endoscopic Instrument Co, Ltd of 62, Shirland-road, London, W 9, for their help and patience in the construction of this instrument

J P Mitchell
M S Lond, F R C.S, F.R C S E
Bristol

AN OBTURATOR FOR FILLING BURR-HOLES

Preoccupied as they are with good functional rather than good cosmetic results, neurosurgeons sometimes forget how serious is the circular depression in the scalp over a burr-hole We take great pains over proper apposition of the scalp edges of a wound, and very often the scar of a former craniotomy would go unnoticed except for an arc of unsightly tell-tale dents

These dents are permanent, and, even if they are covered by hair now, that man may be bald in ten years' time!

Besides the unsightliness there are two very real complications of such depressions First and most important, every stranger notices them, acquaintances point and say "Ooh, what have you had done to your head?", Operations on the head are still almost automatically associated in the lay mind with mental disorder, and from that moment that patient is suspect The second complication is not rare and depends on the propensity of some patients to finger the depressions and to imagine that they are sometimes swollen, or painful, or represent missing brain tissue

After two years' trial at the South-East Metropolitan Regional Neurosurgical Centre I am satisfied that flanged obturators made of nylon (fig 1) are effective and that their use is free from complications It is obviously desirable to have a versatile button-like plug which will fit burr-holes of different sizes, and after some experiments such a size was determined, as regards diameter of plug and width of flange, which would loosely fit into an average burr-hole finished by a no 2 or no 3 Hudson's burr, most commonly used for biopsy or craniotomy The outer surface of the button (fig 2) is ground to a convexity, and the under surface of the flange to a concavity, commensurate with the curve of an average skull, and there is a dimple in the bottom of the button to accommodate a brain nubbin if necessary It has not been found necessary to drill a hole through the centre

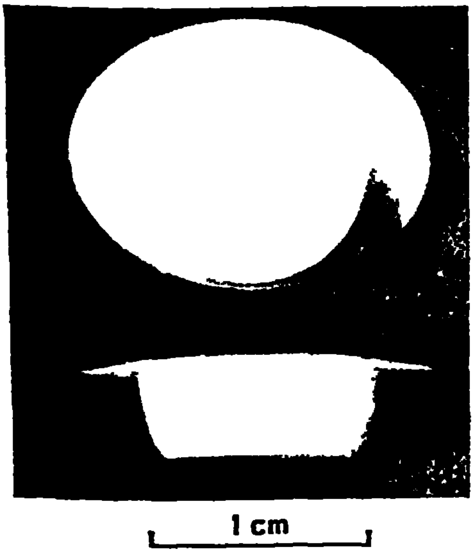

Fig 1—Obturators. Translucency is a rough guide to the requisite thinness of a flange

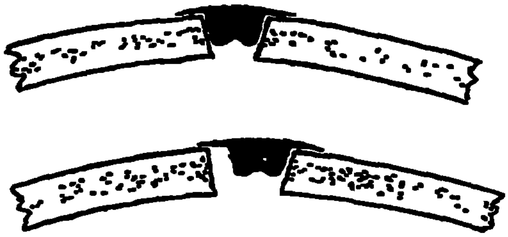

Fig 2—Showing how a single size of button is applicable to a small or large burr-hole

The button is dropped into a burr-hole in bare bone, and secured lightly either by stitching pericranium over it, or by crossing it with a stitch (before adopting this technique I had to remove a button which had been floated out of its hole by hæmorrhage beneath the flap) It is now a routine to insert them into all burr-holes except those deep to the temporal muscle

Properly made with a very thin flange, these buttons are invisible afterwards They are sterilisable by either boiling or autoclaving, are radiotranslucent, and are about a sixth of the price of tantalum discs At present they are made individually on a lathe from nylon rod, but, if the demand warranted it, a steel mould costing several hundred pounds might be made to turn them out in quantity as cheaply as a button in a draper's shop

The obturators have been dubbed "Brook buttons' and are made and supplied by Messrs Allen & Hanburys of London

Brook General Hospital
Shooters Hill Road,
Woolwich

J R Gibbs
M.B Brist, F.R C.S

Steinberg and Gardner[4] showed that white noise masking produces recruitment in the normal ear (In "white" or "thermal" random noise all frequencies are present in equal amounts, producing a hissing sound like escaping steam) Dix, Hallpike, and Hood[5] found that recruitment appears to be associated with damage to the nerve-endings at the organ of Corti but not with damage to the eighth nerve This finding is compatible with the hypothesis that neural noise produces recruitment, for disturbance of the nerve-endings (as in Ménière's disease) would be expected to produce random firing, whereas this is not generally found when fibres are sectioned

When there is marked tinnitus of a particular tone, some loss of hearing is perhaps always found near the corresponding frequency But although tinnitus is often found with nerve deafness it is not invariably found We should not expect it if the deafness was due to a tumour of the nerve, but, if the deafness was due to damage of the end-organ, the patient would presumably be aware of his neural noise as some form of tinnitus If he is not, some explanation is necessary The normal person is aware of a surprising amount of self-generated sound in a silent room, though he is not normally aware of this internal noise It is also true that we are not usually aware of irrelevant regular sounds—e g , the ticking of a clock, and even its chime, when this is familiar, though it may be loud Perhaps in some cases neural noise is rejected in a similar manner, with the result that, although it may tend to mask wanted sounds, there is no awareness of it as tinnitus, at any rate until attention is called to it

We have found it necessary, on quite other grounds, to postulate a "gate" in sensory discrimination mechanisms[6] Perhaps this postulated "gate" is raised to reject abnormally high residual noise The idea of a "gate" is important it is taken over from electronics where the term denotes a threshold introduced into a circuit so that voltages below the gate threshold are rejected The gate may be raised or lowered or may be fixed This suggests a possible connection between auditory fatigue and nerve deafness, and they have many features in common If a sustained noise or tone tends to raise the gate, we should expect recruitment (for only the lower-intensity signals will be affected by the gate) and this is in fact the case Perhaps some of the results obtained by Hood,[7] who has done much work on auditory fatigue, might be interpreted on this hypothesis Further, the neural origin appears to be the same for nerve deafness as for auditory fatigue—between the electro-cochlear activity and the binaural localisation process, according to Wever[8]

In examining the possibility that typical nerve deafness is due to raised neural noise we have compared differential intensity discrimination (short-tone pips against a continuous tone of the same frequency) over a wide range of intensities and frequencies in (1) nerve-deaf ears showing various degrees of impairment and (2) the normal ear in the presence of white noise masking We should expect the curves relating intensity of the tone pip to the continuous tone to be similar for a nerve-deaf ear and a normal ear, subject to added masking noise By determining the level of noise which produces the best fit of these curves we might hope to estimate the effective level of neurological noise in a nerve-deaf ear showing a given impairment Preliminary results are fairly encouraging, in particular we find that the curves are similar in general form These data are shown in figs 1 and 2, from which comparison may be made

If nerve deafness may be caused by raised neural noise a practical conclusion seems to follow To attempt to raise the wanted signal above the residual noise with a linear amplifier (such as a standard hearing-aid) is likely to overload the ear, for it seems clear that there is no abnormal attenuation in the system Now, it has been shown by Licklider[9] and discussed by Miller[10] that almost all the information-content of speech is carried by the changeover points, and almost none at the energy peaks, it thus appears possible to prevent overloading, while retaining the necessary information, by using suitable peak clipping in hearing aids This has been tried but has produced only slight improvement[11] Perhaps in addition it may be necessary to filter out those frequencies where impairment is greatest, because continual stimulation appears, at least in some cases, to increase tinnitus and therefore presumably the amount of neural masking noise

We wish to thank Dr E R F W Crossman, Dr T S Littler, Miss Violet Cane, and Prof O L Zangwill for helpful suggestions and advice We are indebted to Mr A S H Walford for providing nerve-deaf patients from Addenbrooke's Hospital The Medical Research Council gave a grant to one of us (J G W) and a grant for apparatus

R L Gregory
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New Inventions

A SIMPLE RESECTOSCOPE

Modifications of an instrument usually lead to something more complex which requires greater experience in handling The development of the resectoscope from the days of the Stern/McCarthy ratchet-driven instrument is an example of the complexities which can be superimposed on a machine of initially simple design

In the past twenty-five years the demand has been for improvement in vision and illumination, for reduction in the size

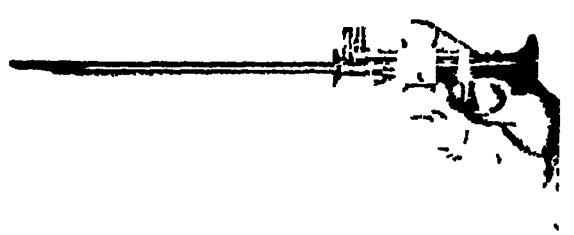

Fig 1

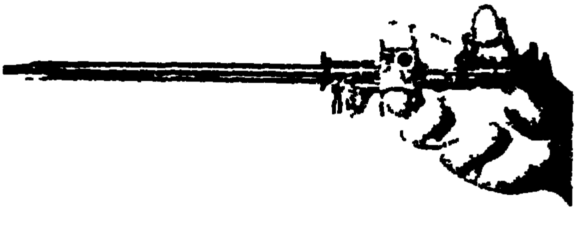

Fig 2

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tosus (D.L.E.) Of 8 cases of D.L.E. 7 were positive for both L.E. cells and the antinuclear factor, and 1, clinically typical, negative in both tests In 3 out of 4 doubtful cases of D.L.E. the antinuclear factor was found. Of 44 sera from rheumatoid arthritis cases, 8 contained the antinuclear factor The L.E. cell test was positive in one of the latter (but the result of this test was available in only 14 of the series) In *Still's disease*, 3 out of 15 cases gave a positive antinuclear factor test, all were L.E.-cell negative. Sera from the following cases were also investigated with negative results acute rheumatic fever (11 cases) convalescent rheumatic fever (7), polyarteritis nodosa (2) dermatomyositis (1), ankylosing spondylitis (1), and doubtful rheumatoid arthritis (5).

In the positive and negative rheumatoid-arthritis group, comparisons were made between extent and activity of the arthritis, sex age, duration, E.S.R., D.A.T. and nodules Middle-aged females with a high D.A.T. and nodules appeared more commonly in the positive group The affinity of the L.E. globulin factor for white-cell nuclei of the rabbit rat, mouse, guinea-pig, chicken and toad had been demonstrated, and in the chicken and toad the nucleated red cells also took up the factor Tissue and white-cell nuclei pretreated with streptodornase fail to take up the factor

Whether the antinuclear factor was responsible for the development of L.E. remained in doubt in vivo the factor was not taken up by the cell nuclei of tissues from patients with L.E., cell nuclei took up the factor only after in-vitro incubation with the patient's own serum Thus, damage to the cell membrane or nuclear membrane seemed to be an essential prerequisite for uptake of the serum factor

Rheumatoid Arthritis of the Cervical Spine

Dr J SHARP, Mr D W PURSER, and Dr J S LAWRENCE reported that X-rays of the cervical spine of rheumatoid-arthritis patients aged 55–64 had been compared with those of individuals in this age-group selected at random from the general population. The features indicative of rheumatoid arthritis appeared to be narrowing of multiple discs, particularly the upper two (with relatively little osteophytosis of the vertebral bodies and a tendency to erosions rather than sclerosis of the adjacent plates), vertebral subluxation (particularly through narrowed discs or at multiple levels), and erosions of apophyseal joints

Using these features as criteria, 427 radiographs taken from random samples of the general population in the age-group 55–64 were examined in an effort to recognise the subjects suffering from rheumatoid arthritis The films were read without knowledge of the clinical or serological findings or of the radiological findings elsewhere.

The prevalence of these changes was found to be 6% in males and 7% in females (in whom the changes tended to be more severe) On comparison with other criteria of rheumatoid arthritis in the population sample, it was found that the cervical changes were significantly associated with positive sheep-cell agglutination tests and also with radiological changes of rheumatoid arthritis in the hands or feet, but only poorly correlated with rheumatoid arthritis as diagnosed clinically Both clinical rheumatoid arthritis and radiological changes of the disease in the hands or feet, however, showed a very significant association with positive sheep-cell tests

These findings suggested that in the general population the disease may be encountered in a form in which the spine was mainly or exclusively involved but which was not diagnosed clinically as rheumatoid arthritis in the absence of changes of rheumatoid arthritis in peripheral joints and that this form of the disease may be important in studies of the prevalence of rheumatoid arthritis in populations since it may account for some apparently "false" positive results in the sheep-cell agglutination test. In clinical practice, rheumatoid involvement of the cervical spine was important both on account of the associated pain, which may be severe, and the resultant mechanical instability, which may lead to severe cord damage.

Reviews of Books

Cortisone Therapy

J H. GLYN, M.D M.R.C.P., D.PHYS.MED., consultant in physical medicine, Prince of Wales and Tottenham Group of Hospitals
London Heinemann. 1957 Pp 162. 21s

THE experience of eight years has not sufficed to define clearly all the indications for the use of cortisone and all its limitations That controversy has not yet been stilled is no reason for denying to those who seek it a convenient source of guidance on the present position of treatment with the hormone or its related steroids Such guidance Dr Glyn has now concisely supplied, in a form that will be widely appreciated.

He has had much experience of cortisone in the treatment of rheumatic disorders and his views are very personal. As Lord Cohen of Birkenhead remarks in a foreword, not all will approve unreservedly of the opinions expressed, but in general these opinions are unlikely to lead the practising clinician far astray In rheumatoid arthritis, Dr Glyn's view is that steroids are strongly indicated in some 10% of cases His reaction to the results of controlled trials, comparing cortisone and aspirin in the treatment of rheumatoid arthritis, is that they served to curb overenthusiasm for cortisone without necessarily casting serious doubts on the wisdom of its use under particular circumstances He holds that individual patients may benefit more from cortisone than from other forms of treatment, and that statistically controlled trials may fail to establish this he tends to accept or reject the evidence of controlled experiment according to whether or not it agrees with his own impressions Thus in discussing whether cortisone is a useful adjunct to manipulation, he is reluctant to accept the negative results of a trial and elsewhere uncontrolled clinical data bearing on the role of steroids in precipitating arteritis are rejected and statistical corroboration demanded. The reader is left in little doubt, however, that opinion on many topics has not yet crystallised, and the practical advice on administration and precautions is very sound. Dr Glyn believes that the dangers of steroid therapy have been overemphasised but he gives a full account of its undesirable effects

In an appendix by Dr J G Bearn, some good anatomical guidance is given on the technique of intra-articular and other forms of local-injection treatment with steroids The book concludes with some suggestions for assessing and recording clinical progress and with a short bibliography

Current Surgical Management

Editors JOHN H MULHOLLAND, M.D., professor of surgery, New York University School of Medicine, EDWIN H. ELLISON, M.D., associate professor of surgery, Ohio State College of Medicine, STANLEY R. FRIESEN, M.D., associate professor of surgery, pathology, and oncology, University of Kansas School of Medicine. Philadelphia and London W B Saunders 1957 Pp 494 70s

WHAT an exciting book this might have been! The editors invited some of the leading exponents of opposing schools of surgical thought not only to air their views but to thrash out their problems in open debate The subjects ranged from the management of acute cholecystitis to perforating wounds of the heart, and they included such controversial topics as the treatment of peptic ulcer regional ileitis, cancer of the breast, cancer of the thyroid, pancreatitis, and burns The list of contributors guaranteed that the opinions expressed, however extreme, would merit a few moments' thought at least

If the hopes thus generated by the contents page had been less high, there might have been no disappointment. Some of the sections are indeed admirable. Blakemore, Garrott Allen, Child, Robert Moore, and A C Singleton on portal hypertension and bleeding oesophageal varices provide the most lavish fare, but there are others almost equally good As a whole, however, the book falls short of expectation. As the editors themselves remark, "what appears on the surface as marked differences of opinion is (often) not so marked when more deeply probed" and much that is stale might have

Medical Societies

THE HEBERDEN SOCIETY

THE annual general meeting of the society was held on Dec 13 and 14 There follow summaries of some of the papers read at the meeting

Phenylbutazone in Rheumatic Fever

Dr G WILL described the treatment with phenylbutazone of 32 cases (19 males and 13 females) of acute rheumatic fever, all fulfilling the modified Duckett Jones criteria 17 patients were of 16 years of age or under, and in 21 it was the first known attack of rheumatic fever 11 patients had been initially treated unsuccessfully with aspirin The maximum daily dosage of phenylbutazone was 600 mg This was given for the first few days and was followed by 400 mg daily for two weeks, then 200 mg daily for a further two weeks

In every case there was a rapid response to treatment Joint pain and swelling were relieved within twenty-four to forty-eight hours and fever and tachycardia settled in three to five days The sedimentation-rate fell steadily to normal levels in all cases it had fallen to 15 mm (Westergren) in one hour or below by the end of the fifth week of treatment In 2 cases premature cessation of treatment was followed by relapse, with subsequent control on resuming treatment with phenylbutazone There was only one serious toxic episode in the series, a melæna 3 patients had mild epistaxis

Pathology of the Rheumatoid Cervical Spine

Dr J BALL said that a characteristic feature of the intervertebral discs of the cervical spine was the presence of a synovial joint—the neurocentral joint—adjacent to their lateral borders *In a postmortem study of 20 cervical spines from* typical cases of rheumatoid arthritis (not selected on clinical or radiological grounds) neurocentral arthritis was found in all but 1 of the 18 cases in which this area was examined, apophyseal joints were involved in 19, in neither was there a preferred site of involvement Disc lesions were often encountered, mainly in the posterolateral and anterolateral parts of the annulus and also along the disc-bone border in these regions Serial sections indicated that the lesions were extensions of pannus arising in the roof or the anterior or posterior recesses of the neurocentral joint In the affected area the annulus was replaced by a granulation tissue whose appearance varied according to the degree of maturation, the occurrence of bone in the posterolateral part of the annulus may represent a quiescent stage of a rheumatoid erosion and may be found in association with bony ankylosis of the corresponding neurocentral joint

Atlanto-axial dislocation was found in 3 cases Dislocation at the first, second, or third disc occurred in 5, and in each instance there was associated erosion of the disc annulus posteriorly, anteriorly or in both sites Appreciable disc erosion was not necessarily accompanied by subluxation, occasionally this could be accounted for by ankylosis of the corresponding apophyseal or neurocentral joint In the single case in which dislocation was severe enough to cause compression of the cord, it was noted that some degree of fixation was present above and below the level of dislocation, due mainly to ankylosis of apophyseal joints

The disc lesions found in the rheumatoid cases were not encountered in the cervical spines of 12 elderly subjects considered not to have suffered from polyarthritis It was also noted that whereas in the control cases disc narrowing and osteophytosis were predominantly located at the fourth and fifth discs, in the rheumatoid cases disc narrowing when present showed no such predilection for the lower discs and was often unaccompanied by conspicuous osteophytosis

Heart lesions in Rheumatoid Disease

Dr B CRUICKSHANK remarked that previous workers had described a variety of non-specific cardiac lesions in patients suffering from rheumatoid disease, and the occurrence of rheumatoid granulomata in the heart was well-recognised, though rare Most of the non-specific lesions had been regarded as rheumatic The whole picture was complicated by the inclusion of examples of ankylosing spondylitis in several of the previous series

Heart lesions, other than those attributable to some other disease, had been studied in 100 patients suffering from rheumatoid disease Rheumatoid granulomata were found in the mitral and aortic rings and cusps in 5 patients and in the myocardium in 1 of these Active rheumatic heart disease was seen once and healed rheumatic endocarditis in 5 patients, in 2 of whom no histological examination was made Non specific chronic endocarditis was seen in 9 patients Although the macroscopic appearances suggested rheumatic endocarditis, microscopic examination failed to reveal characteristic lesions of that disease In 4 of these patients the inflammation was active and diffuse, with many of the features found in rheumatoid lesions elsewhere in the body, though necrosis was absent These were regarded as further examples of rheumatoid endocarditis The other cardiac lesions encountered were myocarditis (10 patients), arteritis (20), and pericarditis (15), all of which were commoner in patients admitted to hospital for treatment of rheumatoid disease than in those admitted for treatment of intercurrent disease In many of these patients tissues other than the joints were extensively involved

The incidence of rheumatic heart-disease was no higher than in unselected necropsy series Rheumatic fever, it was concluded, played no significant part in causing the cardiac lesions of rheumatoid disease, and many of these lesions were part of the rheumatoid process itself

Ulcerative Colitis and Arthritis

Dr B M ANSELL and Dr E G L BYWATERS reviewed all cases of definite ulcerative colitis attending Hammersmith Hospital and the Canadian Red Cross Hospital, Taplow, over the past ten to eleven years The overall incidence of arthritis appeared to be 15% 37 cases of arthritis with proved ulcerative colitis from this source and from patients seen at the Central Middlesex and West Middlesex Hospitals have been studied very closely The knee- and ankle-joints were the ones most often involved and, in contrast to rheumatoid arthritis, hand and tarsal joints were much less often affected There was a relatively high incidence of sacroiliac involvement, and of particular value diagnostically was the swelling of the proximal and distal interphalangeal joints of the toes

In most cases the arthritis was that of a recurrent mild synovitis, gross changes being found in only 4 cases, of which only 2 were typical of rheumatoid arthritis with nodule formation and a positive direct agglutination test (D A T) 29 patients had the Rose test repeated on a number of occasions 25 were persistently negative, the 2 already mentioned were persistently positive, and 2 others positive on one occasion only 8 of the 37 cases had erythema nodosum and this might occur early in the course of their disease or *during an exacerbation* In 7 of these the arthritis was present at the time of the erythema nodosum, and 1 of these patients also had pericarditis

The frequency of the arthritis, its course and pattern, its joint distribution, its frequent association with erythema nodosum, and the negative D A T suggested that it was a separate arthritis from rheumatoid arthritis, due either to the factor that produces the gut lesion or secondary to that lesion, or if it was rheumatoid arthritis it had been considerably modified by the presence of ulcerative colitis

Antinuclear Serum Factor in Connective-tissue Disease

Dr E J HOLBOROW and Dr D M WEIR had examined sera from 100 cases of connective-tissue diseases by the fluorescein-conjugated antiglobulin test for the presence of the antinuclear factor previously described [1] in disseminated lupus erythema-

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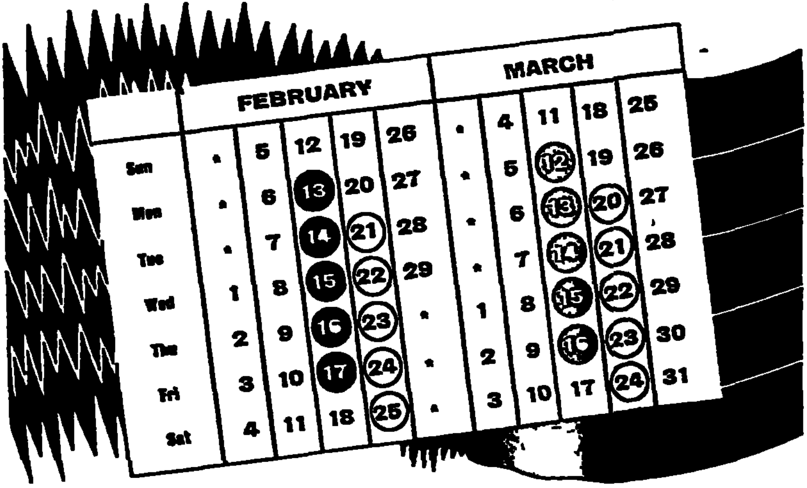
● *Restoring the normal rhythm*



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Diagnosis Obstinate eczema of the face Photograph taken before treatment with F99

Photograph taken after 18 weeks treatment with one "F99" capsule and one application of F99 ointment daily

It has been shown beyond question by large scale serum-lipids studies that a good proportion of patients suffering from intractable skin conditions have a deficiency of the essential fatty acids It is not possible to carry out these studies in everyday practice, but any patient with eczema or furunculosis who fails to respond to symptomatic treatment should most certainly be tried with essential fatty acids ' F99 A high proportion of these patients will be found to respond
In gravitational ulcers, where the skin is 'under-nourished , the application of additional essential fatty acids rarely fails to heal the wound

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THE LANCET

LONDON 11 JANUARY 1958

Sex Reversal

By the "sex" of an individual we may nowadays mean one of several different things—such as the genetic sex, determined cytologically, the gonadal sex, determined with certainty only histologically, the anatomical sex, determined by inspection of the genitalia, the hormonal sex, determined biochemically, the social sex, determined by upbringing, and the psychological sex, determined by behaviour In most of us, of course, all the "sexes" agree but results at any level may be equivocal, and when unequivocal they may disagree with equally unequivocal results at any other level Such discrepancies are only moderately rare, and it begins to seem probable that every possible permutation of discrepancies can occur The older classifications of "pseudohermaphroditism" and the like are no longer sufficient, and there is urgent need of a new terminology And it is, for instance, not really justifiable to limit the term "sex reversal" as Dr Ashley and Dr Jones do in their paper on p 74 to simple discrepancy between genetic sex and all the other "sexes" at the opposite end of the scale transvestitism is equally a sex reversal

Nevertheless, if only because of the light thrown on them simultaneously by nuclear sexing techniques, it is worth considering together briefly the known varieties of extreme discrepancy between genetic sex and apparent sex There are perhaps four chromatin-negative Turner's syndrome (genetic male, gonad neutral, otherwise feminoid), chromatin-positive Klinefelter's syndrome (genetic female, gonad male, otherwise masculinoid), "testicular feminisation" (genetic male, gonad male, otherwise feminoid), and Ashley and Jones' case (genetic male, gonad female, otherwise feminoid) The first two are now very well known, and nuclear sexing, especially by the oral-mucosal smear technique, has so facilitated their recognition that they are becoming almost common [1–7], but the two latter are less familiar

When reported at a meeting last summer, Ashley and Jones' case was in fact the first certain example of its kind to be described there are a few possible earlier cases, but in none is information complete enough for certainty The infant was by all ordinary criteria female there were some minor pseudohermaphroditic features (an enlarged clitoris and a double urethra), but the vagina, uterus, tubes, and ovaries were clearly female, and the ovary had a full complement of ova The only discrepancy is the male nuclear sex In a sense, this is a mirror image of chromatin-positive Klinefelter's syndrome—male gonad and habitus with female nuclei in the one, female gonad and habitus with male nuclei in the other—though it would be unwise to push that analogy too far There will almost certainly be a tendency to regard this as a mere variant of Turner's syndrome Admittedly there is a variety of Turner's syndrome [8 9] in which virilisation occurs to a minor degree, with clitoral enlargement (one can probably blame activity of the Leydig-like hilus cells [10] for this), and the mild pseudohermaphroditic features of Ashley and Jones' case could probably be explained in this way There are also cases of Turner's syndrome in which the ovarian vestige contains a few follicles,[3] and it is just possible that these represent the adult state of Ashley and Jones' case But on the whole it seems better to regard this for the present as a new and separate entity Apart from anything else, acceptance of it as a variant of Turner's syndrome could overturn the whole satisfactory edifice of explanation of that syndrome as a kind of intrauterine castration, for this patient is certainly not a castrate Some distinct mechanism must have been operative, and one can do no more than speculate on its nature

A minor but most interesting point emerges from the case. The nuclear sex, tested at several points, is male, but the polymorphs are female Similar discrepancies have been noted in Klinefelter's syndrome in the opposite direction [11] One may add to this the fact that the characteristic drumstick structures seen in polymorphs in blood-films from females are seen in several animal species—notably the rabbit—in which the sex chromatin cannot be seen in tissue nuclei It is increasingly apparent that Davidson and Smith's polymorph drumsticks are not simply modified sex-chromatin bodies [12] The question now arises, what are they?—a fascinating new problem. Meanwhile, it is clearly no longer sufficient to rely on polymorph sexing in cases of possible sex reversal

The fourth of the sex reversals deserves to be better known, and certainly better considered than in our last brief and partly inaccurate mention of it [13] It is a very well defined syndrome with a considerable literature, which has, we fancy, missed the public eye chiefly for lack of a sufficiently exact name "Male pseudohermaphroditism", variously qualified, is its usual label, but that is too vague and all-inclusive a term Morris,[14] though he did not discover or claim to discover it (he collected 72 reported cases), suggested the term "testicular feminisation", a name at once compact, evocative, and precise, and one which we think (pace Dr Swyer [15]) might well be adopted Essentially the condition consists in the combination of male nuclear sex and testes with a fully feminine external anatomy and endocrine status [14 16 17] (The nuclear sex has of course been determined only in recent cases, but there seems to be no doubt that it is constantly male [18 19] an error in these columns [13] was derived from a misreading of Danon and Sachs' paper [20]) Though many cases present themselves

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1 Polani P Lessof M H Bishop, P M F *Lancet*, 1956 ii 118
2 Grumbach M M, Blanc, W A Engle, E T *J clin Endocrin* 1957, 17, 703
3 Hoffenberg R, Jackson, W P U *Brit med J*, 1957, ii 1457
4 Wiedemann H-R, Tolksdorf, M, Romatowski H. *Ärztl Wschr* 1957, 12, 857
5 *Lancet* 1956 ii 127
6 Nelson, W O *Acta endocr Copenhagen* 1956, 23 227
7 Ferguson-Smith M A, Lennox B Mack, W S, Stewart, J S S *Lancet*, 1957, ii 155
8 Russell, A Levin, B Wilmers M J *Proc R Soc Med* 1955 48 318
9 Greenblatt R B Higdon L *J clin Endocrin* 16 235
10 Sternberg W H *Amer J Path* 1949 25 493
11 Plunkett E R Barr, M L *Lancet* 1956 ii 853
12 Ashley D J B *Nature, Lond* 1957, 179 969
13 *Lancet*, 1957 i 31
14 Morris J M *Amer J Obstet Gynec* 1953, 65 1192
15 Swyer G I M *Lancet* 1957 ii 144
16 Beatty, D C Champ C J, Swyer G I M *Brit med J* 1953 i 1369
17 Schaumkell K W Stange H-H *Arch Gynäk* 1956 37 1449
18 Graham G A, *J Path Bact* 1955 70 516
19 Segal S J, Nelson W O *J clin Endocrin* 1957, 17 676
20 Danon M Sachs, L *Lancet*, 1957, ii, 20

early in life with inguinal herniæ [21]—operation on which results in discovery of the testis in or near the sac—the most striking cases are those found later in life, after they have undergone what seems to be a normal puberty apart from amenorrhœa They then appear, in build, external genital anatomy, breast development, and social attitudes, to be normal women, but they sometimes have moderately eunuchoid proportions, and usually the body hair is deficient Gynæcological examination reveals a blind vagina and absence of the uterus laparotomy shows gonads which may closely imitate ovaries in external appearance and site (though they may descend to the inguinal canal and then give rise to herniæ) but in *histology* are clearly testes They are not normal testes, but then they are not at the normal site of testes, and their abnormalities are, at least chiefly, those constantly seen in cryptorchidism In some cases at any rate they have shown some degree of spermatogenesis,[22] and they have the increased liability to tumour of all abdominal testes It is beyond doubt that these gonads are testes but it is equally beyond doubt that they secrete female hormones, for their removal produces menopausal symptoms and breast atrophy [23]

Often if not always this condition is hereditary, and some remarkable pedigrees are known [22] Though the exact mechanism of inheritance has been [22] and is [20] [24] a matter of dispute, it is evidently transmitted through the female only in affected sibships all, or nearly all, the males become testicular-feminoids, and all the females are normally fertile, half of them being carriers Unless one restricts definition very closely to cases with the completest feminisation, this variety of sex reversal is not very rare and there is a very real need—greater perhaps even than with other varieties—that the doctors who handle such a case in the first place should understand something of its nature (DIEKE [25] gives a vivid illustration of the dangers of vacillation) The discovery of testes must not be made a signal for drastic attempts to change the established sex of the patient nor should the testes be removed—at any rate before the age of 20—for they provide the hormones essential for adolescent development There is a case for their removal later in life, as a potential source of tumours in this respect, and this alone, we can treat them as ordinary cryptorchid testes Quite apart from such practical issues, these cases are of very great interest, and some part of the light which has beaten recently on other types of sex reversal might well be spread to include this variety Guidance would be especially welcome on the prognosis of feminoid children found to have testes early in life may we always assume that these anomalous gonads will produce feminising hormones at puberty, or is there a risk of virilisation, and if so, are there any criteria by which one can recognise the cases concerned? And is it true [21] that these patients not only do not produce their own androgens, but are resistant to therapeutic doses of synthetic androgens?

DR SWYER, who very properly pointed out the errors in our early editorial,[13] took us to task also [15] for saying *that no combination of hormones has yet made an XY* breast secrete milk The example he gives in refutation is a poor one, for Foss [26] produced only a drop of "*colostrum*" from his transvestite—hardly milk He might better have quoted the engorgement with milk produced in male rat breasts by multiple hormone treatment [27] But even that milk did not reach the exterior—it was only halfway secreted There are still *some* limits to what hormones can do to a male breast

Occupation and Compensation

IN the course of a chronic disease many circumstances tend to produce neurosis , and when the disease is occupational, permanent in its effects, sometimes difficult to diagnose, and responsible for a disability often hard to assess, these circumstances are particularly potent Following a discussion on the working of the National Insurance (Industrial Injuries) Act at a recent course on industrial pulmonary diseases at Hammersmith Hospital, correspondents in our columns have emphasised how administrative difficulties influence decisions about benefit claims for pneumoconiosis Critics have pointed to the anomaly where one man severely disabled by chronic pulmonary disease has his claim rejected and another with little functional impairment obtains benefit, to lack of uniformity in the application of the Act in different localities, to overmuch importance attached to X-ray appearances, to failure to use respiratory-function tests, and to the rejection of some applicants without clinical examination after initial scrutiny of chest X-ray films On the other hand, it has been submitted that, though discrepancies arise, the present arrangement works very well within the framework of the law, and that it would be hard to find a better

It is not to be disputed that bronchitis and emphysema are commoner among workers in many dusty occupations than among the general population , and the inference is that some of the increase is occupational On the other hand, bronchitis and emphysema are common in city-dwellers with no occupational exposure to dust or fumes Claimants whose X-ray films show the characteristic changes associated with pneumoconiosis can usually be accepted without question as having occupational disease, but doubt exists in the cases without typical radiological findings As the law stands, bronchitis and emphysema are not pneumoconiosis and so are not compensable Whatever part the X-ray examination may be held to play in assessing the stage of the disease, it is undoubtedly a necessary step in diagnosis The dilemma of the administrators is that the restriction of benefit to claimants with pneumoconiosis as at present defined by law means the rejection of some men and women with chronic pulmonary disease which *may* be of occupational origin, while widening the scope of the scheme would admit to benefit many non-occupational cases

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21 Deamer W C *Amer J Dis Child* 1954 88 497
22 Petterson G Bonnier G *Hereditas* 1937, 23, 49
23 Goldberg M B Maxwell A F *J clin Endocrin* 1948 8, 367
24 Witschi E Nelson W O Segal S J *J clin End* 1957 17, 737
25 Dieke W *Zbl Gynäk* 1956 23 859 (in appendix p 916)
26 Foss G L *J Endocrin* 1956-57, 14 vi
27 Lyons W R Li C H, Johnson R E, Cole, R D *J clin Endocrin* 1954 14, 831 (abstr)

The past twenty years have seen a very considerable widening of the scope of the original Workmen's Compensation Act in regard to industrial pulmonary disease Nevertheless criticisms do not seem to have diminished, and the sense of frustration experienced by rejected claimants, their relatives and workmates, and their doctors, when the disability is strongly believed to be occupational, is hard to dispel Moreover, there is misunderstanding of the functions and the powers of the pneumoconiosis medical panels and of the reasons for rejecting particular claims Further widening of the scope of the Act will do nothing to remove the causes of dispute, but merely extend the limits of controversy The main cause of contention is the considerable difference between the rates of benefit payable in industrial and non-industrial diseases It becomes an important issue for the workman to establish that his disease is occupational in origin It is often impossible to do this beyond doubt it may be easy to exclude an occupational cause if there has been no exposure to dust or fumes, but in a group of workmen occupationally exposed what doctor would undertake to distinguish the occupational from the non-occupational cases of bronchitis and emphysema in the absence of characteristic X-ray findings? The same problem arises in connection with other industrial diseases—notably perhaps, dermatitis—where the difficulty of establishing the precise cause of the disease, and the ensuing litigation, may contribute greatly to the anxiety, depression, and even demoralisation of the sufferer

What is the basis for compensation schemes? Are there valid reasons for paying a higher rate of benefit for an injury or disease arising in the course of employment than for one contracted in the domestic or public environment—for a factory accident than for a street accident, for pneumonia due to accidental exposure to nitrous fumes at work than for pneumonia complicating influenza, for pulmonary disability due to industrial dust than for that contracted through living in overcrowded conditions? Doctors who worked in child-welfare clinics in the 1930s will remember the many infants who suffered from repeated, almost continuous, bronchitis Are they now among the chronic bronchitics of the community, some of them workers in mines or foundries and blaming dust for their condition? Why should a man who chooses to work in an industry with a known dust hazard qualify for a higher rate of benefit if he contracts pneumoconiosis than the equally disabled chronic bronchitic who had no control over the environment which caused his condition? Would not the paying of equal rates of benefit be reasonable?

The widespread feeling of dissatisfaction with the Industrial Injuries Benefit Schemes undoubtedly has its origin in the different rates of benefit payable for industrial and non-industrial illness During the discussion at Hammersmith Hospital Dr A T Doig called attention to the need for examining the position and equating the two rates, and Dr Gilson and Dr Hugh-Jones and their colleagues suggested similar action in their letter of Dec 7

> "Two courses are possible The first is to abandon the rigid attribution requirement [i e, that the disease shall be attributable to the occupation in the individual case] and, in occupations where epidemiological studies have shown an increase in the prevalence of the common diseases, to compensate any disabled man as if all his disability was due to occupation This would remove the injustices which your correspondents claim to exist, but only at the expense of introducing new ones The second requires a fundamental change in approach—namely, to make provision under the National Health Insurance Scheme for adequate benefits for the disabled irrespective of how the disablement has been caused If this were done, epidemiological studies would return to their primary objective—prevention"

The opener of the debate in our columns, Dr Norman Macdonald, also supports this second course in his closing letter of Dec 28 He returns to his early suggestion, which seems to have been lost sight of in some of the succeeding letters, that a fully independent committee or commission should be set up to review the position As he says, the problem has been in the past, and still is, altogether too vexatious and absorbent of time and mental energy, which could be better devoted to preventive measures Its solution would bring a sense of freedom and relief to all concerned

Annotations

GETTING OVER OPERATIONS

As Dr R M Davies told the Section of Anæsthetics of the Royal Society of Medicine last Friday, a patient's need of skill and care following surgery is most acute as he leaves the operating-theatre, for he is then suffering not only from his disease but also from the effects of operative trauma and the residua of anæsthesia Yet at precisely this moment he is likely to be sent on a long journey to a ward, which can in itself be dangerous The particular kind of skill and care he needs cannot be provided consistently throughout the surgical wards, and in Dr Davies' opinion it is best concentrated in a single ward where all patients should stay for a while immediately after operation This ward should be very near the theatre, so that long journeys are avoided and the surgeon and anæsthetist can get quickly to the patient if necessary

Mr J R Belcher, and other speakers who followed him, were generally in agreement with these principles, but Mr Belcher thought that more emphasis should be placed on recovery before the patient leaves the theatre No patient, he thought, should leave the theatre till he is breathing well and reasonably conscious, and warm if he has had hypothermia In the discussion, nobody spoke against recovery wards or disputed Dr Davies' contention that they save lives, as his experience with 33,000 patients at East Grinstead shows Some thought that not every patient should go through a recovery ward, but, as Dr Davies said, the anæsthetist cannot tell in advance which patients are going to be in trouble As regards the ideal size and organisation of such a ward, most speakers agreed that this must vary with the type of hospital Patients who have metabolic difficulties (e g, after hypophysectomy) or have had unusual operations (e g, involving a cardiopulmonary bypass) may need special provision Skilled nursing is essential and a day-

and-night service highly desirable, especially since emergency patients are the ones who stand in most need of recovery rooms The ward, it was felt, should probably be in the charge of an anæsthetist, and a resident in anæsthetics act as the house-physician The nurse in charge should have the rank of sister and should remain in the ward for several months in some hospitals with recovery wards the student nurses spend short periods there, which gives them experience they would otherwise miss because the patients are no longer treated in general wards, but in others the ward is staffed by part-time qualified nurses from outside the hospital In a hospital which has many scattered theatres, a choice must be made between concentration of skill and apparatus, on one hand, and proximity of the recovery ward to the theatre on the other Most speakers favoured proximity, if a choice must be made, though the answer might be different if nurses were scarce

Prof E A Pask felt sorry for the patient who had been in the general ward long enough to get used to the staff, and awoke after operation in strange surroundings Other speakers had found that patients do not mind this, if they have been told beforehand, and indeed welcome the solitude in which they awake Some thought that the patient should spend the day before operation in the recovery ward, this would be hard on the patient at the bottom of the operating-list, who will see his predecessors return laden with drips and tubes and perhaps vomiting, but would avoid much of the nocturnal turmoil of general wards where emergency patients are admitted Perhaps the ideal would be to admit night emergency patients to the recovery ward before operation, but other patients only after operation Patients should stay in the recovery ward for as long as it will benefit them—which may be for minutes or for days

Dr G F Rawdon Smith feared lest the development of recovery wards should lead to yet another specialty Professor Pask replied that this warning came too late, for in France there is already the *réanimateur*, and doubtless he will come to Britain with the Common Market

KURU

THE discovery of a new disease has the same fascination as the identification of a new element or a new planet Four years ago Patrol-Officer J R MacArthur reported a strange endemic disorder in a newly explored area south of Mount Michael in the Eastern Highlands of Australian New Guinea He wrote " I observed a small girl sitting down beside a fire She was shivering violently and her head was jerking spasmodically from side to side I was told that she was a victim of sorcery " This trembling disease (it was called *kuru*), with its preference for females and its fatal outcome, had been known to the Fore tribe, who now number about 11,000, as their special curse for at least twenty years, and it had been observed by Berndt in 1952 and 1953 in them and adjoining peoples Extensive investigations were undertaken by Zigas and Gajdusek, who with commendable enterprise established a kuru research centre at the Okapa patrol post Their first reports [1] [2] record their findings in 150 cases

The disease, which has been observed at ages from 5 to " over 40 ", is confined to the Fore people and to members of contiguous tribes intermarrying with them It is, for instance, unknown in the neighbouring Kukukukus who have no marriage contacts with them and who are cut off by the formidable barrier of the Lamari river, but it has arisen in several members of a substantial party of Ingarias who migrated from the western slopes of Mount Michael, later to intermarry with the Fores The disease has also been reported, however, in a few women from communities with a low kuru incidence after entry into a kuru region, and this fact has to be satisfactorily explained before this can be accepted as a genetically determined disease The male/female ratio is 1/5 42, and in 23% of the observed cases the patient's age was less than 15 About 1% of the total population is at present affected, but in certain localities this figure may reach 10%, indeed, kuru sometimes accounts for half the deaths in a community

The onset is insidious, with ataxia ("loose knees"), but about a third of the patients have prodromal symptoms (not, so far, observed)—knee pains, headaches, malaise, fever, cough, and coryza, in order of frequency, but never an acute illness As the ataxia progresses a distinctive tremor appears, irregular but fine, involving the head, trunk, and limbs, it is aggravated by excitement, fatigue, or attempts at voluntary movement It tends to subside during relaxation and disappears during sleep In the second and third months the tremors coarsen and interfere with work and sleep, but the state of nutrition remains good Choreiform jerks with wild athetotic movements may appear, especially when the patient tries to stand Emotional behaviour may be prominent, paroxysmal hilarity alternating with moods of depression By this stage the patient has to use a stick for support while attempting her daily work, but soon she is forced to sit and has to be carried to the pig feasts and other tribal ceremonies A progressive dysarthria sets in and often a convergent strabismus, a flexed posture, and a parkinsonian facies Soon she is confined indoors, mute and doubly incontinent, and rapidly succumbs to starvation, decubitus, or some intercurrent infection

The course of this disorder is from three months to two years or more, with an average of six to nine months Although it is almost always steadily progressive, in 2 cases remissions have been observed (two in 1 case) followed by relapses, 2 presumed instances of the disease were noted to appear and remit with the menstrual cycle Kuru, which is apyrexial throughout, does not interfere with pregnancy and there are no physical signs other than those referable to the central nervous system The fundus oculi is normal and the pyramidal tracts are not involved The cerebrospinal fluid has revealed no abnormality except an occasional positive Lange curve Increases in the β-globulin and sometimes the α-globulin in the serum, when observed, have had to be discounted because they may be noted in New Guinea highlanders unaffected by kuru Immunological, therapeutic, and chemical studies, including some on copper metabolism, are so far negative

Pathological findings are confined to the nervous system, where preliminary observations point to a widespread neuronal degeneration with neuronophagia, the parts most affected being the cerebellum and extrapyramidal system and, to a lesser extent, the anterior horn cells, the inferior olives, thalamus, and pontine nuclei

The Fore people live in a heavily forested terrain, covered with kunai grass, at an altitude of 5000–7000 feet No toxic substance in the diet, water, soil, or body paints, or anything else in the environment has been found to account for the condition. In fact the evidence is so far in favour of some genetically determined degeneration of the central nervous system, and this is supported by the facts that kuru has been known to develop in several siblings at the same age and that the disease may show the phenomenon of anticipation. A congenital tremor has been seen in two Fore natives and occasional instances of parkinsonism are known in adjacent territories, but these conditions are easily distinguished from kuru. Further information on this striking disease will be awaited with interest, for it may well serve to throw welcome light on unsolved problems of neuropathology.

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[2] Zigas V, Gajdusek, D C Med J Aust 1957, ii, 745

MEASUREMENT OF BLOOD-PRESSURE IN INFANCY

ALTHOUGH determination of the blood-pressure is not always regarded as a part of the routine examination of infants and children,[1 2] more conditions are now being recognised in which a dependable method of estimation is necessary.[3] For clinical purposes, one of the usual cuff methods (using auscultation, palpation, or oscillometry) can generally be applied, even to newborn babies, and Holland and Young[4] succeeded in measuring the systolic pressure in premature infants weighing as little as 4 lb by palpation of the brachial artery. The estimation must be made while the infant is quiet, which may mean waiting until he is asleep, or giving a sedative. By comparing the results with those obtained by direct intra-arterial measurement, Robinow et al.[5] showed that if a cuff of suitable width is used (2.5 cm. for newborn and 5 cm. for older babies) sufficiently accurate readings of the systolic pressure can be obtained by ordinary clinical methods, though there are errors in the diastolic readings because of difficulty in hearing the Korotkow sounds. The use of an amplifying stethoscope may make auscultatory determination both easier and more accurate. Where the conventional methods are unsuccessful, the "flush" technique of Gaertner[6] may be used. It depends on the production of reactive hyperæmia by deflating a cuff from a pressure of 300 mm. Hg, at a rate of about 5 mm. per second, on a limb made relatively bloodless distally by compression with an Esmarch or similar bandage. The limb is held at heart level and watched in a good light, and the pressure at which the first flush appears is noted. Since this method was first used in infants by Cappe and Pallin[7] and by Goldring and Wohltmann,[8] a number of reports on it have appeared,[9–12] and it has become an established clinical method.[13]

Average figures for normal brachial pressures in newborn babies are 80/46 mm. Hg, for babies aged six months 89/60, and at one year 96/66,[14] but the flush method gives values 10–20 mm. lower than systolic pressures obtained by palpation, auscultation, or direct measurement—i.e., it gives approximately mean pressures. The arm pressure is normally given as a few mm. higher than the leg by this method,[8] but in 8 cases of coarctation of the aorta the difference was 36–88 mm.[12] The flush method takes longer than conventional methods of sphygmomanometry, and is more likely to make babies cry; but even if they do, according to Forfar and Kibel,[10] an error of only 7–10% is introduced. Schaffer[15] wrote "the flush method is simple but coarse and unreliable," and it is undoubtedly inferior to auscultation when the sounds can be well heard. It is useful, however, for babies whose brachial pulses cannot be felt, and for femoral blood-pressure estimation in suspected coarctation of the aorta.

F.A.O.

A SMALL book[16] sets out in simple language the problems that the Food and Agriculture Organisation of the United Nations has faced in the first twelve years of its life. These problems still exist, for, as the director-general, R. B. Sen, says in his foreword, "there are today millions of hungry people, there are unused resources, maladjustments of distribution, depressed rural population." Nevertheless, the record is heartening, for F.A.O. has proved a good means of spreading knowledge in underdeveloped countries. The greatest difficulty in its way has been that of getting the necessary cooperation between Governments, especially in economic matters: too narrow a nationalism remains an important hindrance to scientific development. But it is significant that the Governments of the various countries of North Africa have never been so united—or so effective—as when serving as members of the Desert Locust Control Committee, sponsored by F.A.O. National political wisdom may grow on a diet of international scientific knowledge.

NEW YEAR HONOURS

SIR Harry Platt was knighted six years before he became president of the Royal College of Surgeons, and the baronetcy now bestowed on him recognises his three years' tenure of that great and strenuous office, as well as the value, in all his capacities, of his vigour and freshness of mind. The particular reason for Sir Stewart Duke-Elder's promotion to be a knight grand cross of the Victorian Order is presumably his services to the Royal Family, but these are of course only one manifestation of his remarkable services, through ophthalmology, to medicine. Of the new knighthoods, two, in the Order of the British Empire, are conferred on the recently appointed heads of the medical departments of the Royal Navy and the Royal Air Force, Rear-Admiral R. C. May and Air Marshal P. B. Lee Potter. Three of the knights bachelor work in Australasia (Dr. H. R. R. Grieve, Mr. W. G. D. Upjohn, and Dr. Ralph Whishaw) and three in Great Britain. Of Professor Krebs, of Oxford, Nobel prizewinner of 1953 and discoverer of the citric-acid cycle, it has been said that as a leader and teacher he has instilled the element of genius that turns possibilities into realities. Dr. Kenneth Cowan has retained and increased the confidence of his colleagues by his understanding work as chief medical officer of the Department of Health for Scotland. Dr. Bentley Purchase's championship of the difficult office of coroner, as well as his outstanding labours in it, deserve the honour they now receive. These are only the first names of a list which brings forward, for public thanks, much notable work—some of it widely known but much of it done in places where only a few colleagues can be aware of its quality.

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Points of View

A PLASTIC APPROACH TO SURGERY

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CONSULTANT PLASTIC SURGEON, THE LONDON HOSPITAL, E 1

THERE is no such thing as a "lucky" surgeon—"the wind and the waves are on the side of the ablest navigator" To be lucky is to know the rules and to know when to break them

The first rule is that diagnosis should precede treatment, and to disregard this rule is "worse than a crime, it is a mistake" The word "diagnosis" is merely a verbal symbol to represent a living and changing phenomenon, diagnosis in its fullest sense is an understanding of the pathological process present The making of a diagnosis is a continuous process which does not cease with the start of the operation, but should always be one step ahead of the treatment It is fatal to cling to an incorrect diagnosis, so, having made a diagnosis, do not stick to it A plastic outlook is essential Each case should be treated on its own merits, since no two cases are the same The man with a rigid method and technique is dangerous if he says that something is always so, he is either teaching or no surgeon Since pathological processes change, what was a correct diagnosis at one time may be wrong later One should start an operation with a working diagnosis, together with a clear conception of the known facts and an open mind

One learns quickly from one's own mistakes, sometimes too quickly It is nicer to learn from the mistakes of others However, it is essential to be able to recognise a mistake, and it may be hard to realise that the result might have been better Inquisitiveness is an essential attribute of a good surgeon, because inquisitiveness leads to an increase of knowledge, and to know all about a *condition is to know its complications, and thus avoid them*

Do not ignore the opinion of the uninstructed, for rude minds sometimes contain pearls of wisdom, and discussion is always helpful, because what is dark when unspoken may become clear when discussed

Although the diagnosis is correct, it may be difficult to decide on the treatment, because this so much depends on the prognosis The knowledge of the prognosis of a disease and the assessment of the prognosis in the particular case is essential in deciding the treatment, especially in carcinoma

So often the problem *is not how to do the operation,* but what operation to do, since it is the duty of the surgeon to prolong living in comfort, rather than to prolong the discomfort of dying A clear conception of why one is operating at all, and why the particular operation has been decided upon, should always be kept in mind

You should not do today in an ill patient what can be done tomorrow or later in a fit patient Emergency operations should be avoided, if possible the acute abdomen, for instance, is a Pandora's box of mischief To an already ill patient do not add the insult of a big operation, *he needs a life-saving operation, and no more* Do not try to paint the lily, for a live weed is better than a dead lily

* * *

The gentle handling of tissues is essential, this rule must not be broken Avoid lethal surgery, whether it is a cell or the patient that dies The more dead or dying cells left in an operation site, the slower the recovery The heavy-handed surgeon who mauls tissues, often with the aid of fierce instruments and retractors, is the one who complicates already elaborate techniques in a vain attempt to reduce the incidence of postoperative sepsis

There must be no tension, either in the surgeon or in the tissues Healing is quickest when the tissues lie adjacent to one another without tension or compression Both these states, which are associated with tight stitching, upset the blood-supply to the healing edge Sutures should *be inserted in such a way that the blood-vessels in the loop* of the stitch are not compressed, either at the time of stitching or later when the tissues swell from postoperative œdema otherwise more trauma is caused, with more œdema and more compression Whereas a ligature is for *hæmostasis, a suture is to approximate tissues until they* heal, and a stitch that is inserted to perform both these functions is essentially bad The stitch that sutures the transverse mesocolon to the stomach in the posterior Polya gastrectomy should be tied so loosely that even if the middle colic vessels are contained in its loop, they are not obstructed The stitch that sews the peritoneal layer but inadvertently pierces the gut lumen will not slough out Often the leakage of intestinal contents results from a stitch obliterating the blood-supply to the suture line I remember a surgeon who, his muscles bulging as he tied his sutures, said "I can never understand why my colporrhaphies break down—I tie my stitches tight enough"

Each stitch must be inserted and tied as if it were the most important one Since a successful operation depends on its weakest stitch, each one should have meticulous care *As is seen in skin suture, a badly placed stitch* cannot be corrected by any number of rightly placed stitches, so it should be removed at once If the stitches are loose and soon removed, only the incision will be visible, and not the stitch marks But stitches can be removed early only if there is no tension and a good blood-supply On the face, for instance, stitches can be removed in three days, but where the blood-supply *is bad, as on* the back, they may have to be left in for fourteen days

By your scars will you be judged—the patient honours the surgeon if the scar is neat, for if the internal malady is cured, what is left save the scar by which to judge the result? *A neat suture line may cover a multitude of sins* Incisions should be made in the direction of Lange's lines, *which for the most part lie in the flexion creases If a circle* is drawn on the skin, and the circle of tissue is removed, the resultant bare area is larger than the area removed, and is oval in shape, showing that tension, and unequal tension, exists in the skin Therefore, if the incision is made at *right angles to direction of the least tension* a good scar results, if it is made in another direction there may be a contracture

"I shall excise the scar, the whole scar, and nothing but the scar, so help me Hippocrates", is the initiate oath of the plastic surgeon The resulting defect is sometimes surprisingly large—one removes a pennyworth of scar and gets a shillingsworth of bare area This is due to the fact that, where the skin is supple, skin defects heal by the contracture of the scar tissue drawing the edges together, rather than by epithelial growth

* * *

Nature abhors a vacuum, and fills it with a blood-clot, and, as hæmatomata are almost synonymous with wound infection, subcutaneous dead spaces can be obliterated by end-on mattress sutures of non-absorbable material with the loops tied over packs Some sites are more prone to the formation of hæmatomata than others Whereas blood-vessels in the face usually stop bleeding naturally, those in the lower abdomen do not, so every miserable bleeding blood-vessel must be ligated In plastic surgery, pressure dressings are used to press the graft against the recipient area and so prevent hæmatomata The introduction of the crêpe bandage has been the greatest advance in skin-grafting in the 20th century To control hæmorrhages, pressure dressings should be left for four days Six days shall you labour and the seventh is for the evacuation of hæmatomata

Raw surfaces should not be left exposed, because they granulate and form scar tissue Scar tissue is feminine in gender, being perverse at all times it contracts when it should relax, as in strictures, and stretches when it should contract, as in hernia repairs To say that a wound is granulating well is a contradiction in terms If, in transplanting a ureter into the colon, it is allowed to prolapse into the lumen, so that the epithelium where the ureter is cut is not in contact with the epithelium of the colon, the outer surface of the ureter will granulate, forming a circular scar which contracts around the ureter and causes urinary obstruction, sepsis, and death, even if the ureter is put into a defunctioned loop of bowel there will still be stricture leading to urinary sepsis Whitehead's operation for hæmorrhoids fell into disrepute because tension and sepsis led to the separation of the bowel mucous membrane from the skin, and the circular scar led to stricture formation Some surgeons wonder why their colostomies stenose when they do not suture the mucous membrane to the skin, but the wonder is that stricture is not commoner

* * *

The best dressing for any raw surface is a skin graft, and the thicker the graft the less the contracture Repeated dilatations are the signposts of surgical failure, and pull-through methods of anastomosis are bad The failures of prostatectomy, immediate and delayed, are failures to get immediate epithelial cover

Hippocrates said, "Do not operate on growths—it makes them worse", the same rule holds today One should operate on the normal tissues away from the growth, and not cut across carcinomatous tissue For the surgeon, the way to hell is paved with short incisions, for the patient the way to heaven is paved with small excisions, particularly in carcinoma surgery Carcinomata are seldom removed completely, but the growth of those cells that are left behind is held in check by many factors As the radiotherapist depends on the tissue reaction of the healthy patient for the treatment of carcinoma, so does the general surgeon The cynic says that in every case of carcinoma of the breast, recurrences will develop provided the patient lives long enough But the early recurrence appears in the patient who has made a slow postoperative recovery Therefore she should be kept as fit as possible before, during, and after the operation Large operations should be avoided wherever possible, because they lessen the general health of the patient and so upset the hormonal control At the site of successfully treated carcinomata, plastic operations should be avoided lest they liberate carcinoma cells from the scar tissue

* * *

To be a quick operator is good, but speed must never be gained by the sacrifice of any principles Thou shalt not worship speed for its own sake, for it is a false god A quick surgeon never hurries, for speed is not made by overhaste when you drive a car, a high average speed depends not on how fast you go, but on how slowly you don't go Delay is due to indecision, which results from incorrect diagnosis, faulty planning, and lack of experience The repetitive, unproductive movement should be avoided, as in time-and-motion study the hand that puts down the scalpel picks up the artery clip—in one movement Time is saved by attention to many details, such as the position of lights, trolleys, and assistants, and by teamwork Time is saved, therefore, by performing slow, deliberate, economical movements, never unnecessarily repeated Thus, speed becomes the handmaiden of the surgeon and not his mistress

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Public Health

INFLUENZA IN LIVERPOOL

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CITY OF LIVERPOOL

The spread of influenza from North China and Hong Kong last spring has been reported from many areas (Mulder 1957, Fawdry 1957, Guthrie et al 1957, Lim et al 1957) We describe here its arrival and spread in Liverpool, and compare its course and effects with those of the last sharp outbreak, which attacked Merseyside in January, 1951 (Semple 1951)

Influenza in 1957

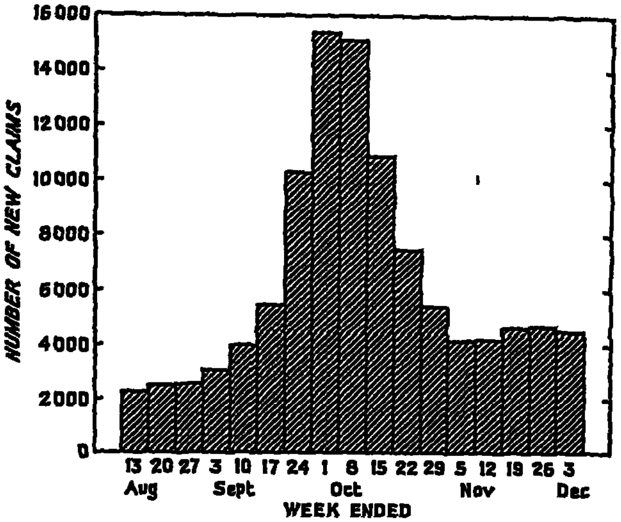
The first influenza patient to reach Liverpool arrived in the s s *Clan Chattan* from Calcutta on June 27 4 more cases were reported in another ship from India on July 1 There was then a break of seven weeks until August 19, when 27 patients arrived in the s s *Hellenes* from South Africa From then until the end of October, 35 ships docked carrying a total of 455 people with influenza The most heavily infected ship was an Indian naval vessel which docked on Aug 27, with 252 cases of influenza aboard

The outbreak in Liverpool started early in September It seemed to be at its height on Sept. 27 and 28

Incidence

The spread of the epidemic was studied day by day by collecting information from as many sources as possible, including the first sickness-claim forms, school absences, and sickness returns from industrial firms in the city and from the Liverpool Passenger Transport Department

The school absence figures rose quickly to a peak on Sept 27 when the average sickness-rate was 39 6% for infant schools, 40 2% for junior schools, and 50% for senior schools The



City of Liverpool Weekly new claims for sickness benefit, 1957

high incidence was found equally in all areas of the city The highest rates were among the older children—a finding unusual in widespread illness of a relatively mild nature Such findings were also noticed in the large independent schools of the city These independent schools started their term about three weeks later than those of the local education authority, and the peak of attack was also about three weeks later, in early October

TABLE I—DEATHS FROM INFLUENZA, PNEUMONIA (INCLUDING BRONCHOPNEUMONIA), AND BRONCHITIS

Week ended	No of deaths (all ages)					
	Influenza		Pneumonia		Bronchitis	
	1957	1956	1957	1956	1957	1956
Aug 31	—	—	12	11	4	1
Sept 7	1	—	19	8	6	15
Sept 14	—	—	11	13	6	11
Sept 21	—	—	6	6	5	2
Sept 28	6	—	22	15	11	13
Oct 5	18	—	19	13	16	11
Oct 12	25	—	29	11	14	12
Oct 19	21	—	21	7	10	9
Oct. 26	11	—	42	5	25	4
Nov 2	5	—	14	—	9	14

The new claims for sickness benefit collected by the Ministry of Pensions and National Insurance rapidly increased (see figure) Daily figures of new claims from three local offices of the Ministry were telephoned to the health department The peak of these first sickness claims (see figure), representing the highest incidence in adult insured workers, came in the weeks ending Oct 1 and Oct 8 The peak in adults was therefore a week to ten days later than that in the schoolchildren Figures collected from industry showed similar trends The daily sickness-rates of three large firms (comprising the passenger transport department, a football-pools firm [employing mainly women], and a large mixed factory) were

Date	*Sickness* (%)	*Date*	*Sickness* (%)	*Date*	*Sickness* (%)
Sept 16	8 2	Sept 28	14 9	Oct 11	12 0
„ 17	7 6	„ 30	12 2	„ 12	13 7
„ 18	8 6	Oct 1	13 3	„ 13	11 9
„ 19	8 2	„ 2	13 1	„ 14	10 7
„ 20	8 3	„ 3	11 5	„ 15	9·9
„ 21	10 9	„ 4	14 2	„ 16	9 7
„ 23	11 1	„ 5	16 2	„ 17	9 9
„ 24	11 6	„ 6	15 2	„ 18	10 3
„ 25	11 5	„ 7	13 1	„ 19	7 2
„ 26	10 0	„ 8	12 2	„ 20	8 6
„ 27	12 4	„ 9	12 7	„ 21	8 3
		„ 10	10 6	„ 22	8 2

12,500 employees are represented By Sept 16 the sickness-rate was already as high as 8 2%, but it reached its peak on Oct 5 with 16 2% An interesting feature of the outbreak demonstrated by these figures was how slowly the absentee-rates in industry returned to normal

TABLE II—COMPARISON OF MORTALITY AND MORBIDITY IN LIVERPOOL IN 1951 AND 1957

Week of epidemic	No of deaths from				National Insurance new sickness claims	
	Influenza		All respiratory disease			
	1951	1957	1951	1957	1951	1957
P−4	—	—	38	16	2958	3038
P−3	—	1	43	26	2518	3979
P−2	2	—	48	17	1571	5469
P−1	16	—	60	11	9806	10 286
P	85	6	301	39	22,320	15,324
P+1	202	18	476	53	11,447	15,079
P+2	114	25	286	68	6081	10 871
P+3	50	21	118	52	3704	7433
P+4	—	11	89	78	3792	5378

P, " peak week " of highest incidence (not mortality)

Mortality

Mortality figures are given in table I, with the corresponding figures for the same period in the previous year Deaths reached their peak in the week ending Oct 12, when they numbered 25 The number of deaths from bronchopneumonia

TABLE III—INFLUENZA EPIDEMICS, 1951 AND 1957 NO OF DEATHS IN AGE-GROUPS

Week ended	Age (yr)	0-1		1-14		15-54		55-64		65-75		75 –		Total	
	Outbreak	1957	1951	1957	1951	1957	1951	1957	1951	1957	1951	1957	1951	1957	1951
Sept 14, 1957 Dec 23, 1950	Total	6	20	1	10	14	28	26	40	37	72	43	74	127	244
	Influenza	—	—	—	—	—	—	—	—	—	—	—	2	—	2
	Other pneumonias	—	3	—	3	—	1	1	3	3	7	7	8	11	25
Sept 21, 1957 Dec 30, 1950	Total	8	13	5	2	21	48	17	56	32	86	37	96	120	301
	Influenza	—	—	—	—	—	2	—	5	—	7	—	2	—	16
	Other pneumonias	—	3	1	1	—	1	1	1	1	5	3	7	6	18
Sept. 28, 1957 Jan 6, 1951	Total	5	18	2	7	26	84	40	121	45	218	54	210	172	655
	Influenza	—	—	1	1	—	8	4	12	—	37	1	27	6	85
	Other pneumonias	—	4	—	3	3	9	4	13	4	27	11	25	22	81
Oct 5 1957 Jan 13, 1951	Total	7	22	2	12	38	106	41	155	63	273	63	326	214	894
	Influenza	—	1	1	—	8	27	4	35	2	58	3	81	18	202
	Other pneumonias	—	7	—	3	2	13	4	13	4	33	9	42	19	111
Oct 12, 1957 Jan 20, 1951	Total	7	15	1	6	34	52	44	90	62	177	60	241	209	591
	Influenza	—	1	—	—	9	13	3	22	10	33	3	45	25	114
	Other pneumonias	3	7	—	—	4	3	3	10	7	15	12	33	29	69
Oct 19, 1957 Jan 27, 1951	Total	3	12	2	4	23	43	46	40	58	98	66	125	199	322
	Influenza	1	—	—	—	3	4	6	5	8	19	3	22	21	50
	Other pneumonias	—	—	—	1	1	2	4	3	6	7	10	13	21	26

and pneumonia continued to increase the high level of 42 in the week ending Oct 26, compared with 5 in 1956 This lag between the peak period for incidence and deaths is usual, but there did seem in this outbreak to be a rather longer period of increased respiratory deaths, though they at no time reached exceptional levels

The weekly mean temperature during the peak of the epidemic was between 52°F and 54°F This represents a level about 1 5°F below the mean temperature for the time of year—a much smaller variation from normal than during the 1951 outbreak

Comparison of 1951 with 1957

The outbreaks of 1951 and 1957 were remarkably similar in size but very different in effect (table II) The sickness first claims were very similar in the four peak weeks of the outbreak in 1951 there were 49,654 claims, compared with 52,560 in 1957 The incidence in children, however, was greater in 1957

The peak of the 1951 outbreak was at the start of a school term, but the absence-rate in the first two weeks of that term (coinciding with the peak of the outbreak) in all schools in Liverpool was 17 7% In the 1957 outbreak, the maximum absence-rate for the two peak weeks was 23 1% This difference is greater than is apparent because the epidemics were at different times of the year In the 1951 epidemic, the absence-rate was 17 7% in early January, when the normal figure would be 12 2%, and in the 1957 epidemic the rate was 23 1% compared with a normal figure for late September of 8 3%

The most striking differences were in the death-rates (table III) The number of deaths from influenza for the six worst weeks in 1951 and 1957 were 469 and 81 respectively The figures for the worst single week are even more striking—202 deaths in 1951 compared with 25 in 1957 These findings are repeated to a less extent with the "other pneumonia" deaths, 329 in 1951 and 143 in 1957

There is evidence that the 1951 epidemic attacked a much larger proportion of older persons in the community in 1951 the old persons' homes in the city were very heavily attacked, whereas in 1957 they almost entirely escaped (only 33 cases of a population of 1351 old persons in the hostels) This would account to some extent for the much lower mortality-rate in 1957, but the season of attack must also have played a part in reducing mortality in 1957

It would be interesting to know whether, in 1957, people over 50 years old escaped illness because they had already been exposed—perhaps in 1918—to a virus of similar strain [1] Perhaps this question can be answered by observing what happens in January and February, 1958, if a second wave appears

Summary

The large influenza A outbreak in Liverpool in September/October, 1957, is described and compared with a similar influenza A outbreak in 1951

Numerically the outbreaks were similar, but in 1951 there was a much higher death-rate and evidence of many older persons being attacked In 1957, the outbreak was much milder and attacked young people, especially schoolchildren

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[1] Since this account was written, the virus responsible for the recent outbreak has been isolated as A/England/660/57, and is of Asian type

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THE PUBLIC HEALTH IN 1956

Chief Medical Officer's Report

A YEAR ago[1] we quoted Sir John Charles' pleasant account of the weather of 1955, and predicted a less happy account for 1956 In his report on the health of England and Wales for that year,[2] Sir Charles tells of the London fog of Jan 4–7 and the thousand extra deaths that followed it, of the "summer" ("no summer since 1880 was colder and wetter and duller"), and of the fog that covered the country from Dec 19 to Dec 23 But, as he points out, man adapts himself to extremes of climate, and the death-rate remained steady at 11 7 per 1000, the infant-mortality rate reached a record low level of 23 7 per 1000 (though the rate of 14 0 in one borough indicates that there is room for improvement), and the number of deaths due to pregnancy and childbirth (including abortion) was 399, the smallest number on record (toxæmia is responsible for many of the deaths, and for much of the perinatal mortality)

THE CANCERS

The heading of the chapter on the malignant diseases is now given a title in the plural, to signify the growing belief that it is more useful to regard them as a group of diseases with a common link rather than as a single disease Some industrial cancers have been almost eliminated, and knowledge or suspicion of the causes of many other cancers gives hope that their incidence may eventually be reduced

The number of cancer-registration bureaus is increasing, this will help to give a truer picture of the morbidity, as distinct from the mortality, of the cancers, but at present trends can be discerned only from the death-rates The comparative mortality index shows the change in the death-rate from a disease, compared with the rate in 1938, corrected for changes in the size and age-structure of the population at risk, it is a better guide to long-term changes of prevalence than the uncorrected numbers of deaths The index for cancer steadily increased in men from 1 0 in 1938 to 1 17 in 1956, in women it steadily decreased to 0 91 Compared with 1955, the total number of deaths from cancer increased by 775 in men and 595 in women In men the number of deaths from most gastro-intestinal cancers declined, and most of the increase was due to cancer of the lung (794 deaths), prostate (225), bladder (61), and lymphatic and hæmopoietic tissue (53) In women the striking increases were in cancer of the lung (120 deaths), breast (85), and uterus (82), and in leukæmia (85 deaths) The incidence of leukæmia has risen more sharply in the past 25 years than that of any other disease except coronary thrombosis and lung cancer, though part of the increase may be apparent, and attributable to better diagnosis The part played by radiation in its cause has been convincingly shown in survivors of atomic-bomb explosions and in patients treated for ankylosing spondylitis, and less definitely in radiologists and in children whose mothers were radiographed during pregnancy But post-irradiation leukæmias have been chiefly acute or myeloid rather than lymphatic, whereas chronic lymphatic leukæmia has contributed much to the increase, and the proportion of cases of leukæmia in which radiation can be definitely incriminated is small

Deaths from lung cancer continue to increase in number (from 1955 to 1956, by 5 4% in males and 4 9% in females) Though in certain occupations (the mining of radioactive ores, the refining of nickel, and the manufacture of asbestos, chromates, and coal-gas) the workers have an increased risk of lung cancer, the two main causal factors against which evidence is substantial are cigarette-smoking and atmospheric pollution Many reports confirm the association between cigarette-smoking and lung cancer—particularly the squamous-celled variety Figures obtained from the mortality among doctors indicate that, even for heavy smokers, the risk of lung cancer developing is lessened if smoking is given up, habitual smokers are deprived of the consolation of "it's too late to stop now" Sir John comments "It's never too late to mend!" The Government have undertaken to see that the public are kept informed about this relationship Urban life, with its exposure to a polluted atmosphere, may be the explanation of the higher incidence of lung cancer in New Zealand among recent immigrants from Britain than in non-Maori natives

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[1] *Lancet* 1956 ii 1302

[2] Report of the Ministry of Health for the year ended Dec. 31, 1956 Part ii On the State of the Public Health H M Stationery Office Pp 262 9s

CLEAN AIR

Lung cancer is only one of many disorders attributable, in part at least, to atmospheric pollution Sir John welcomes the Clean Air Act of 1956, which sets up a council to advise on clean-air policy, increases the powers of local authorities over the emission of industrial smoke, and empowers the Minister of Housing and Local Government to declare smoke-control areas, thus easing the burden on local authorities These measures may help to dissipate what Evelyn called "the hellish and dismal cloud of seacole" over our cities Meanwhile fog-masks can be prescribed under the National Health Service, and in London certain hospital beds are reserved for patients suffering from the effects of fog Warnings are broadcast when serious fog is predicted

MENTAL ILLNESS

Admissions to hospital for mental illness increased by 5341 to 88,189, but the number in residence fell by 1353 to 149,219 64,011 mental-deficiency patients were under care Outpatient attendances increased from 714,014 to 762,072, many treatments, including shock, psychotherapy, and abreaction are now given in outpatient departments, and more emphasis is now being placed on keeping patients out of hospital For many patients, day hospitals, night hospitals, or short-term inpatient care is best, but others still need long-term admission Even "chronic" patients can often be reclaimed and sometimes return to society Physical treatments (including tranquillising drugs) have helped to make group re-education and occupation possible The result has been that more and more wards have been unlocked—every ward in several large hospitals Patients who formerly vegetated in confinement can now move freely, enjoy recreation, and undertake employment

Mentally deficient children who have to be cared for in institutions may suffer from being deprived of their mothers In some hospitals nursing assistants or older girl patients (under supervision) have acted as substitutes Where possible children are sent home for holidays, conversely, children cared for at home may be admitted for short periods to give the parents a break

Medical officers of health are increasingly acknowledging their responsibilities in preventive psychiatry, through the maternal and child-welfare, school-health, and health-education services

ACCIDENTS

Another responsibility of the local authorities lies in the prevention of accidents, particularly in the home Health visitors and public-health inspectors, in particular, are in a position to detect hazards in the home and suggest remedies. 6908 deaths resulted from domestic accidents, 688 of them in children under 5 years and 5039 in people over 64 Since 1951, the number of deaths has increased in old people and fallen (by 26%) in the under 5's A survey quoted in the report indicates that less than a third of home accidents are caused by environmental factors (bad design, or, more often, lack of maintenance) Some people are accident-prone, thus an American transport company transferred 5% of their drivers with high accident-rates to static work, the number of accidents then fell to a fifth

There has been no decrease in the fatalities from clothing catching fire A British Standards specification for a fireguard (B S 2788), published in 1956, provides for fixation to the wall by hooks and provision for refuelling and removing ash with the guard in place Cellulose materials (especially cotton, flannelette, and winceyette) and flowing garments (especially stiffened underskirts) present the greatest hazard Materials with an anti-flame finish are on sale The report does not deal with transport or industrial accidents

TEETH

In their reports, very many school medical officers have expressed concern at the poor and deteriorating state of children's teeth The increasing scarcity of dentists draws attention to the importance of two ancillary dental workers—the hygienist and the dental nurse The Dentists' Act, 1956, permits the employment of hygienists in private practice (formerly they were confined, in this country, to the Forces and the public-health service), their work is scaling and polishing, and instruction in care of the teeth Dental nurses, now confined to New Zealand, are employed in the public-health service, where their work is the conservation of children's teeth The 1956 Act provides that the "Privy Council may direct the General Dental Council to conduct an experiment in their training and use"

As experiments in North America have shown, fluoridation at optimal levels reduces the liability to decay, and fluoridation experiments are in progress in four areas of England and Wales The experiments involve the periodic examination of 12,000 children, at the first examination over 90% had dental caries

DISABILITIES

During 1956 the total number on the blind register increased by 1336 to 96,019 These are persons "so blind as to be unable to perform any work for which eyesight is essential" 3 6% were totally blind and 11 1% had perception of light only In 80% of cases the cause is unknown The cause of retrolental fibroplasia was made known in 1953, but the incidence in children aged 0–2 in 1954–56 was half that in 1951–53,* altogether 47 cases were registered in 1956

The prevalence of otitis media has been much reduced, and the commonest cause of deafness in adults is otosclerosis This can often be treated successfully by operation or a hearing-aid A much smaller all-transistor aid should be available soon

Congenital deafness, even if not total, may make a child seem backward, and a scheme has been devised whereby children may be tested in the first year of life early training may give the child a better chance of overcoming his handicap

The demand for artificial limbs does not abate 82% of amputations were for disease, chiefly arteriosclerosis and diabetic gangrene, 13% of the patients with disease had cancers Trauma, most commonly industrial and motor-cycle accidents, accounted for 18% of the amputations Training is a particularly important part of the work of artificial-limb centres Patients as old as 90 have been successfully fitted, 50–60% of patients over 60 became fully independent

INFECTIOUS DISEASES

Typhoid fever "*no longer constitutes a public health problem*", though occasional cases arise, some from infected cockles But the number of cases of dysentery, nearly all Sonne, increased by a third to 49,009 Most cases were mild (there were 33 deaths) and conurbations were affected more than rural districts 11,000 cases of food-poisoning were reported to the Registrar General, but 18,500 came to notice through local health authorities and hospitals These represented 7713 incidents (8961 were detected in 1955), and 44 people died (22 with *Salm typhimurium* infections) Processed and made-up meats were the prime vehicles

Measles was in its biennial phase of minor incidence, and the low fatality ratio (0 2 deaths per 100 notifications) suggests that its killing power is weakening

There is a growing demand for laboratory investigation of virus diseases This is more time-consuming and costly than bacteriological investigation 819 strains of poliomyelitis virus were isolated and typed, but "this represents only a fraction of what will be required if our knowledge of viruses is to be rendered adequate for the purposes of clinical identification and for the development of methods of epidemiological control " Except for smallpox and now poliomyelitis, the control of virus diseases has so far proved impossible Of the lately discovered agents, the adenoviruses were identified more often, sometimes in cases where non-paralytic poliomyelitis had been diagnosed. Types 1, 2, and 5 are usually found in tonsils or adenoids, and types 3, 4, and 7 in association with acute febrile respiratory illnesses The evidence suggests that they are not at present of great epidemiological significance, but vaccines prepared from them have been found to reduce the incidence of respiratory infections in troops There was another, much smaller, outbreak of encephalomyelitis at the Royal Free Hospital, and there were small outbreaks and sporadic cases elsewhere with no deaths There were 173 notifications of "acute encephalitis" with 106 deaths 137 deaths were ascribed to poliomyelitis Virological tests indicate that many cases notified as non-paralytic poliomyelitis (1483 out of a total of 3200 in 1956) were really cases of Coxsackie or other virus infections A beginning was made in the large-scale immunisation of children, 140,013 were given two injections

In 1956 there were no deaths from smallpox and 8 (the lowest figure recorded) from diphtheria The proportion of babies vaccinated in various county boroughs ranged from 2 7% to 74 9%, and of babies immunised against diphtheria from about 30% to 70% The size of the immunisation index seems to depend more on the enthusiasm and vigilance of the local health authority than on family and social attitudes (The occurrence of 2 cases of smallpox in 1957 indicates that the danger still exists) B C G vaccination is being given to increasing numbers of people, especially schoolchildren, a promising new freeze-dried vaccine has been under trial In this country, however, the spectacular decline in deaths from tuberculosis, and now notifications (deaths decreased by 17% and notification by 7% from the previous year), is to be attributed less to vaccination than to epidemiological methods (such as the detection, isolation, and treatment of infected persons and examination of contacts) and effective treatment, especially chemotherapy An encouraging feature of the decline in notifications is that it is most evident in the younger age-groups, which augurs well for the future The highest death-rates from tuberculosis are now in the age-groups 65–69 for men and 75–79 for women

Chemotherapy is also largely responsible for the fall in the fatality ratio of meningococcal infections (now steady at about 18%, perhaps because many cases are missed in the early stages), and for much of the fall in the number of new cases of venereal disease since the peak year, 1946 (by about 80% for syphilis and 60% for gonorrhœa) But after reaching low levels in 1955 and 1954 respectively, both these diseases are now becoming commoner, as are non-gonoccocal urethritis in men and trichomonas vaginitis in women Most infections are not in immigrants or prostitutes Gonorrhœa " is clearly not under control, and one reason for this has been the tendency to play down its importance by over emphasising the power of penicillin it now seems likely that in some areas strains of gonococci partially resistant to penicillin may be coming into circulation "

Sir John refers also to the "perplexing problem" of staphylococci resistant to antibiotics, which are dangerous in their own right and, by producing penicillinase, enable hæmolytic streptococci " to resume their former place as public enemies No 1 of the operating theatre " He attributes the increasing proportion of resistant strains to the indiscriminate use of penicillin in unsuitable conditions

THERAPY

Sir John makes few comments on treatment, but indicates some further examples of its misuse Thus, though some tranquillising drugs are undoubtedly useful in the treatment of severe psychoses, they may give rise to severe and even fatal toxic reactions, and are often disappointing in the treatment of the simple common emotional disorders for which they are very often prescribed

702,593 bottles of blood were issued by the regional transfusion centres in 1956—6% more than in 1955 and 90% more than in 1949 " It seems possible that part at least of the increase is caused by a less discriminating use of transfusion, and it is difficult not to conclude that some transfusions are given unnecessarily " This would be serious enough if the only disadvantage of excessive transfusion were the dangers of the method and the cost of the necessary organisation, but it seems that we are near the point where a further increase in demand will not be met by an equivalent increase in the donor panel 12% of the blood collected was contributed by British and American Forces stationed in this country

Infectious Diseases in England and Wales

Disease	Week ended December			
	7	14	21	28*
Diphtheria	1	3	2	5
Dysentery	576	669	610	419
Encephalitis				
Infective	1	—	3	2
Post-infectious	—	1	2	2
Food-poisoning	146	128	160	95
Measles, excluding rubella	2214	2450	2435	2022
Meningococcal infection	29	34	27	19
Ophthalmia neonatorum	14	19	22	16
Paratyphoid fever	6	11	9	4
Pneumonia, primary or influenzal	649	778	703	755
Poliomyelitis				
Paralytic	61	53	33	21
Non-paralytic	20	18	18	2
Puerperal pyrexia	188	233	166	138
Scarlet fever	723	795	683	576
Smallpox	—	—	—	—
Tuberculosis				
Respiratory	510	507	467	301
Meninges and C N S	7	6	7	1
Other	65	39	35	28
Typhoid fever	3	—	2	4
Whooping-cough	575	504	452	257

*Not including late returns

Medicine and the Law

Is Automatism a Defence to Crime ?

In recent years much of the discussion on criminal responsibility has centred on the death penalty for murder This particular controversy will no doubt abate now that there is the defence of diminished responsibility and the death penalty has been abolished for certain murders, but there remains both scope and need for further medicolegal discussion of the element of intention in criminal liability The case of Hill *v* Baxter [1] raised—but left unsettled—the question whether automatism is a valid defence to a criminal charge

The defendant had been charged with dangerous driving The magistrates concluded that, after a certain point, he was not conscious of what he was doing, and inferred that he was then incapable of forming any intention as to his manner of driving They therefore dismissed the charge On the prosecution appealing, the Lord Chief Justice said that the magistrates evidently meant that the driver was in a state of automatism His Lordship observed that there was no case in either English or Scottish law in which the defence of automatism had been set up or been the subject of judicial decision In the present case, his Lordship was content to rest his judgment on the ground that there was no evidence which justified the magistrates' finding that the defendant was not fully responsible in law for his actions, and that his intention was immaterial because the prohibition against dangerous driving was absolute Mr Justice Devlin also thought there was no need in the present case to determine just what part automatism played in liability for crime, it was a novel point and the answer would depend, among other things, on the nature of the liability which the prosecution had to establish

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[1] *Lancet*, Jan. 4 1958, p 47, *Times*, Dec 20, 1957

In establishing criminal liability, the question of intention may enter in what the lawyer regards as two different contexts One basic rule applies to all criminal offences—namely, that the accused must have committed an act prohibited by the law or he must have omitted to do something required by the law Furthermore, this act or omission must have been voluntary An involuntary act or omission is one which is not willed, and Halsbury's *Laws of England* give the following examples

> " an act done by a person in a state of unconsciousness, as in sleep, or by a person of such tender years or in such a state of idiocy or insanity that he has, or is deemed to have no mind and therefore no will, or by a person who is constrained by overwhelming force An act or omission is voluntary in this sense if it might have been avoided by the exercise of reasonable care "[2]

In the case of many criminal offences, it is also necessary that the accused should have been guilty of a legally blameworthy condition of mind known as *mens rea* This element is essential in all the common-law crimes with one exception, but is not regarded as essential in some statutory offences Thus, as the Lord Chief Justice pointed out, in the offence of dangerous driving the intention of the driver is immaterial, even an honest error of judgment may render a motorist guilty of dangerous or careless driving Where *mens rea* is an essential element, proof of guilty intention rests in the first place upon the prosecution, in many cases, however, the facts themselves will raise a presumption that the accused had a guilty intention, in which case it will be upon him to rebut the presumption

It would seem—particularly from Mr Justice Devlin's judgment—that a plea of automatism might be relevant in establishing that an act or omission was involuntary in the sense considered above, or in disproof of *mens rea* where this is an element in the offence In either case, it would seem obligatory upon the defence to produce some evidence of automatism, though the degree of proof might vary according to the nature of the defence If the defence is that the act or omission was not "voluntary ", the court might require a higher standard of proof than in a case where the defence is a denial of *mens rea*

Medical Reports in Criminal Proceedings

In civil proceedings the use of agreed medical reports is a recognised practice which saves both time and expense One would suppose that a similar procedure could be adopted in criminal cases, but apparently this is regarded as improper In Hill *v* Baxter[3] a bench of magistrates considered the charge of dangerous driving The defence produced two letters from a doctor dealing with the defendant's condition, the prosecution had no objection to these letters and they were accepted by the magistrates This procedure was condemned by the Lord Chief Justice Agreed medical reports, he said, have no place in criminal courts, where evidence must be given on oath and be subject to cross-examination unless there is a statutory exception allowing documents or certificates to be put in

Special Articles

NEW YEAR HONOURS

The list of honours published on Jan 1 contains the names of the following members of the medical profession

Baronet

Sir Harry Platt, M S Lond, M D Manc, F R C S
Lately president, Royal College of Surgeons of England, emeritus professor of surgery, University of Manchester

G C V O

Sir Stewart Duke-Elder, K C V O, M D, D SC St And, F R C S

K B E (Military)

Air Marshal **Patrick Brunton Lee Potter**, C B E, M D Sheff, Q H S
Director-general, Royal Air Force Medical Services

Surgeon Vice-Admiral **Robert Cyril May**, C B, O B E, M C, F R C S, Q H S
Medical director-general of the Navy

Knights Bachelor

Kenneth Cowan, M D Belf, M R C P E, Q H P
Chief medical officer, Department of Health for Scotland

Herbert Ronald Robinson Grieve, M B Sydney
Member of the New South Wales medical board

Hans Adolf Krebs, M A Cantab, M D Hamburg, F R S
Whitley professor of biochemistry, University of Oxford, director of the Cell Metabolism Research Unit, Medical Research Council

William Bentley Purchase, C B E, M C, M B Cantab
Coroner, H M Household and northern district of London

William George Dismore Upjohn, O B E, M D, M S Melb, F R C S, F R A C S
Consulting surgeon, Royal Melbourne Hospital

Ralph Whishaw, C B E, M B Sydney, F R C P, F R A C P
Physician, Royal Hobart Hospital, Tasmania

C B. (Military)

Major-General **Douglas Bluett**, O B E, M B Dubl, Q H P

Air Vice-Marshal **Frederick Elvy Lipscomb**, C B E, M R C S, Q H P

Surgeon Rear-Admiral **Eric Thomas Sutherland Rudd**, C B E, M B Dubl, F R C S E

C.M G.

Donald Dixon McKenzie, M B N Z, F R C S, F R A C S
Senior surgeon, Auckland Public Hospital

C B E (Military)

Group-Captain **Hugh Cuthbert Sutcliffe Pimblett**, M D Durh, R A F

C B E (Civil)

Alexander Brown, M B Edin, F R C P E
Professor of medicine, University College, Ibadan

Trewavas Pearce Eddy, M R C S
Director of medical services, Sierra Leone

Gordon Lilico, M B Edin
Lately a principal medical officer, Ministry of Health

John Campbell McIntyre Matheson, D S O, M B Glasg
Principal medical officer, H M Prison, Brixton

Lambert Charles Rogers, V R D, F R C S, F R A C S, F A C S
Professor of surgery, University of Wales

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[2] 3rd ed vol 10

[3] *Times*, Dec 20, 1957

Seymour Cochrane Shanks, M D Glasg , F R C P
Director, X-ray diagnostic department, University College Hospital, London

Clarence Edmund Smith, L M S Singapore
Assistant director of medical services (tuberculosis), Singapore

Lieut.-Colonel George Henderson Stevenson, O B E., M C , M B Edin , F R C S E
Lately chairman, executive committee, British Red Cross Society (Scottish branch)

Edwin Alfred Trim, O B E , M D Cantab
Director of medical services, Uganda

O B E (Military)

Surgeon Lieut.-Commander David Geoffrey Dalgliesh, M R C S , R N

Squadron-Leader John Ernsting, M B Lond , R A F

Lieut.-Colonel Charles McNeil, M B Cantab , R A M C

O B E (Civil)

Frank Richard Ashton, M B Edin
Medical superintendent, Nethersole Hospital, Hong Kong

Charles Bowesman, M D Dubl , F R C S E
Formerly specialist (surgery), Ghana Ministry of Health

Harold Crawford, M B Melb , F R A C S
Orthopædic surgeon, Children's Hospital, Brisbane

Katherine Mary Hirst, M B Lond
A senior medical officer, Ministry of Health

Thomas Victor Humphreys, M B Belf
Lately first secretary and medical officer, H M Embassy, Moscow

Reuben Jacobson, M B W'srand
Director of medical services, Basutoland

Leonard Ross Mallen, M B Adelaide, J P
Medical practitioner, Lower North District, South Australia

Pan Tsoh Chen, M B
For social welfare services, North Borneo

Ivan Samuel Parboosingh
Senior medical officer, Jamaica

John Patrick Sexton, M B Edin
Regional senior health officer, Northern Region, Nigeria

Clarence Edmund Smith, L M S
Assistant director of medical services (tuberculosis), Singapore

Joseph Stanley Thomas, M R C S , J.P
General practitioner, East Ham

Thomas James Russell Warren, M B Dubl , F R C.S E
Director, Samaritano Hospital, São Paulo

Philip Randal Woodhouse, D S O , M C , V D , M B N Z
President, New Zealand Catchment Boards' Association

M B E (Civil)

George Francis Nicholas Anderson, M B Dubl
Senior medical officer, Iraq Petroleum Company in Qatar

Elizabeth Abimbola Awoliyi, M R C P I
Medical officer, Federation of Nigeria

Abraham Johannes Petrus Coetzee, M R C.S
Chief medical officer, Rhokana Corporation, Northern Rhodesia

George Millar Edington, M D Glasg
Formerly specialist pathologist, Ghana Ministry of Health

Irene Elizabeth Beatrice Ighodaro, M B
For social welfare services, Western Region, Nigeria

Frank Stanislaus le Merle
Lately medical practitioner, Basra

Latima Kamya Musoke
Medical officer, Uganda

Olive Hope Robertson, M B Edin
President, Federation of Women's Institutes, Southern Rhodesia

James Scott Robinson, M R.C S
District medical officer, Dominica, Windward Islands

Cyril Augustus Wallace, M B Belf
Medical officer, Tanganyika

In England Now

The reminiscences of the elderly can be tedious, but those of Uncle Edward, now rising 93, have a stark simplicity which amply repay the annual visit Last year's was about the benevolent rat he had once observed piloting its blind mate along a gutter by means of a straw held between its teeth This year Uncle set the ball rolling by remarking innocently that he had just received a Christmas card from Eric Little "He has sent me one regularly for over fifty years" So we dutifully asked who Eric Little was But Uncle was not to be hurried It appeared that in 1887 when he was senior obstetric officer at his alma mater a colleague in practice nearby had sent him an S O S because he was having difficulty in delivering the baby of an elderly primigravida "And no wonder," said Uncle, "because it was not an ounce under twelve pounds" However it appeared that Uncle was quite used to landing twelve-pounders, and he was soon able to hand the baby over to the gamp and turn his whole attention to the mother who was having repeated convulsions which were rather worrying Here again Uncle's skill prevailed, though it was some two hours before his unspecified therapeutic efforts were rewarded, and he could turn once more to the baby "But the baby is dead, Doctor, it was born dead" "Nonsense," said Uncle, "where is he?" It transpired that the baby had been tidily wrapped in brown paper and deposited on top of the dustbin Uncle lost no time in retrieving his charge and divesting it of its make-shift shroud "It certainly looked white and was not breathing, but through my stethoscope I could hear the heart, ten beats to the minute and very muffled" So Uncle, undismayed, proceeded vigorously to apply a method, again unspecified, of resuscitation, which, he avers, is known in the hospital to this day as MacGillicuddy's method of reviving the apparently dead For the third time his virtuosity was crowned with success The baby turned blue, then breathed, and finally bellowed "And soon I was able to place Eric Little in his mother's arms, and hence the Christmas card No, no, his mother never told him the truth—she simply said it was a miracle." Uncle ended modestly

* * *

Well 1958 has certainly come in with a bang There's the geophysical jamboree at the Pole, there's Sputnik I hourly getting nearer, and above all Mr Fairbrother has pain in his chest on exertion Antarctic news has not unnaturally left most people cold, Sputnik I is best forgotten, but Mr Fairbrother's catastrophe has hit the great British Public where it hurts most It stands to reason that if a hero of the Light Programme gets pain on climbing hills and is to have a E C G then something is bound to happen After all what is good enough for him is good enough for the Common Man and the next thing we will find will be our dyspeptics scorning our mag trisilicate and demanding specialists and E C G s galore The Light was friendly when I phoned to plead for a change in the story before Mr Fairbrother was actually in extremis It saw my point It thanked me for phoning, but it promised nothing

That night one of my coronaries sprang an embolism Next evening two had relapses It may mean nothing, but perhaps it does

* * *

In Calgary the Christmas and New Year campaign against people who drive cars when they are not fit to do so is again being widely advertised,[1] and once again the police will DRIVE-YOU-HOME if you are "impaired" and ask for help No names will be named, and no charges will be laid This campaign has helped greatly to lessen the recurring toll among merrymakers, and this year the men who man the *petrol* pumps are going to help by offering coffee and doughnuts *free* along with the gas and oil at service-stations in Regina and Saskatoon, and probably in Calgary as well They hope that the fluid balance will be so well maintained that nobody will be tempted

J R No.
2315

TICK-BORNE MENINGOENCEPHALOMYELITIS IN SWEDEN

SIR,—During recent years cases or epidemics of meningoencephalomyelitis caused by agents related to the Russian spring–summer/louping–ill group of tick-borne viruses have been reported not only from Russia but also from Czechoslovakia,[1] Hungary,[1] Slovenia,[2] Austria,[2] Poland,[3] Sweden,[4] and Finland [5]

The first verified Swedish cases were in the summer of 1954 When, in 1956, again a large proportion of the cases of aseptic meningoencephalitis in Stockholm were found to have been tick-bitten, an enlarged study was undertaken This time tissue-culture methods were adopted for the assay of neutralising antibodies and for the production of complement-fixing antigen The results so far obtained seem to be of some general interest

At first we tried the virus-cell system introduced by Oker-Blom [6]—i e , a strain of louping-ill virus adapted by him to give cytopathic changes in cultures of HeLa cells In our laboratory, however, this virus strain caused only late and partial changes, which varied too much to be used for quantitative tests The cytopathic effect was not much better on KB cells Detroit-6 cells[7] were, however, found to be considerably more sensitive, the changes appeared earlier, were more extensive, and were reproducible The response of the cultures was the same following 12 passages of the virus Actually, a suspension of a mouse brain infected with a strain of louping-ill virus (kindly supplied by Dr F O MacCallum) that had never been carried in *tissue-culture gave as clear-cut cytopathic changes Moreover,* the titre was the same (*$10^{-7\ 5}$* per ml of the 10% suspension) in Detroit-6 cultures, and following intracerebral inoculation into three-week-old Swiss mice

The stationary-tube cultures of Detroit-6 cells used for all neutralisation tests were grown out on a medium of Parker 199 with 40% human serum and maintained on bovine amniotic fluid fortified with 10% horse serum and 0 5% bactotryptose Serial dilutions of serum were tested against a constant dose (1000 TCD_{50}) of virus, the mixtures being incubated at 37°C for one hour before inoculation This dose of virus caused obvious microscopic changes within three days, the final reading of the neutralisation tests was made six or seven days after inoculation A complement-fixing antigen that could be used without further treatment was prepared in Roux flask cultures *Guineapig serum* was, however, substituted for the horse serum in this instance as the antigen otherwise became anticomplementary

Neutralisation and complement-fixation tests were performed on the sera from 159 patients with the clinical diagnoses of aseptic meningitis, meningoencephalitis, or poliomyelitis, who were treated at the Hospital for Infectious Diseases in Stockholm during the latter half of 1956 Neutralising antibodies were found in the convalescent sera of 66 patients, and complement-fixing antibodies in 65 of these *Moreover,* significant rises in titre (at least 4-fold) were found in the convalescent sera of 26 patients, most often with the complement-fixation test On the other hand, none of 44 healthy blood-donors in Stockholm had neutralising antibodies against louping-ill virus About 70% of the patients with antibodies reported that they had, within a couple of weeks before their disease, been bitten by ticks when on vacation somewhere in the Stockholm region during June-September The corresponding figure for patients without antibodies was only 6% The tick *Ixodes ricinus,* a known vector of this virus, is common in Sweden The probability that a tick-borne virus, related to the Russian spring-summer/louping-ill group, caused the disease in the majority of patients with such antibodies is strengthened by the fact that no indications of other virus infections were found in this group Thus no agents cytopathic for human embryonic lung cultures were recovered from stool specimens, and, furthermore, the complement-fixation reaction with heated poliovirus antigens (which responds quite broadly also to infections with several other enteric viruses, such as ECHO 6[8] and ECHO 9), was consistently negative or gave only minimal titres On the contrary, the 93 patients lacking antibodies against louping-ill virus included 25 excretors of enteric viruses (11 polioviruses and 14 other cytopathic agents) and 7 cases of mumps, high and often rising complement-fixation titres against heated poliovirus antigens were also common in this group

The following clinical data have been computed from all 66 patients having antibodies against louping-ill virus The clinical picture corresponded well with that described in Central European tick-borne encephalitis

Thus 75% had a diphasic course The incubation-*period*—i e , the interval between a single known tick bite (28 cases) and the first onset of disease—varied between two and fourteen days (mean six days) The prodromal stage lasted for two to twelve days (mean six days) It was characterised by moderate fever, headache, and muscle pains After a free interval of two to twenty-five days (mean eight days) *the major disease followed Dominant symptoms* were now high fever (lasting for five to twenty-two days, mean eleven days), splitting headache, neck rigidity, and vomiting About half the patients had at least some clinical sign of encephalitis, such as disturbance of sleep, mental confusion, somnolence, vertigo and/or ataxia Not less than 44 of the 66 patients had, however, a definitely pathological electro-encephalogram during the first week and lasting for one to four weeks 17 patients had transient paralysis (5 shoulder and/or upper arm, 1 shoulder and leg, 2 leg, 3 eye, 2 facial, 1 pharyngeal, 3 intestine or *bladder) Lumbar puncture on admission revealed a moderate* pleocytosis with *mostly lymphocytes* and a relatively high protein content

1 of the 66 patients died three weeks after onset of the meningoencephalitis The convalescence of the others lasted between two and fourteen months (in 75% four months or less) The main complaints were the common ones after an encephalitis—i e , headache following mental or physical stress, disturbance of sleep, and inability to concentrate and to memorise

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THE NEW CHINA

SIR,—May I correct two statements in Dr Fox's account of the New China (Nov 9)?

On p 938 he says that " in the various medical colleges of the 1930s and earlier, teaching was usually in English but sometimes in other foreign languages, and the profession was disunited thereby " This implies that all medical colleges taught in a foreign language, which was usually English Actually, although some of the better-known colleges, such as the Peking Union Medical College, did all teaching in English, a considerable number taught in Chinese The West China Union University, with which I was associated, and Cheeloo University, both did almost all their teaching in Chinese These were two of the more important Christian medical colleges in China It is true that some English was used—e g , for hospital histories—but lectures were almost entirely in Chinese The fact that China today has a medical terminology is due very largely to the efforts of missionaries, and Causland's *Medical Lexicon* is still being reprinted in China

Also on p 938 is the statement " I am told that after graduating in arts, qualification as a doctor took eight years and qualification as a nurse took five (which meant that too few nurses stayed the course) " Both statements are quite untrue, as a reference to the calendar of the Peking Union Medical College will show The entire course (premedical, medical, and one year of internship) took eight years Three years premedical, taken in any suitable university but usually in Yenching University, then four years of medicine (as in the U S A), followed by one year of rotating internship was the total requirement for medical qualification in the P U M C At the

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1 Sinkovics, J Die Grundlagen der Virusforschung Budapest, 1956
2 Grinschgl, G *Bull Wld Hlth Org* 1955, 12, 535
3 Przesmycki, F , Taytsch, Z , Wroblewska, Z, Semkow, R , Stanczyk, R Kamieniecka, Z , Kirkowska, I , Kicinska, H *Ann Inst Pasteur,* 1956, 91, suppl 1
4 Svedmyr, A., Melén, B , Kjellén, L *Acta med scand* 1956, suppl 316, 20
5 Oker-Blom, N *Ann Med exp Fenn* 1956, 34, 309
6 Oker-Blom, N *ibid* p 199
7 Stulberg C S , Berman, L , Ruddle, F H *Proc Soc. exp Biol , NY* 1955, 89, 438
8 Von Zeipel, G , Svedmyr, A *Arch ges Virusforsch* 1957, 7, 355

end of the first year of medical studies, Yenching University usually conferred a B SC degree—that is after three years in Yenching and one year in the P U M C The total requirement of West China and of Cheeloo was seven years, and of almost all other medical colleges in China it was six As for the nurses, the P U M C certainly did not require an arts degree before entry The total length of their nursing course—a degree course—was five years In nearly all other schools of nursing the course was three years in length, and no degree was given The P U M C nursing course was specially designed to train a relatively small number of future principals of schools of nursing, nursing superintendents (matrons) of hospitals, &c

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LESLIE G KILBORN

THE REINFORCEMENT OF TENDON-REFLEXES

SIR,—Dr Penman (Jan 4) raises the interesting question of the effective stimulus for reinforcement We do not think that the "alerting" if unaccompanied by the effort of muscular activity is sufficient For example, in fig 3a of our paper the subject had been warned to be ready to grasp as soon as he felt the hammer blow That he was fully alert is shown by his short reaction time, yet there was no reinforcement On the other hand, we have noticed that some subjects tense their muscles as soon as they are alerted and we suspect that the effort involved in this movement accounts for the anticipatory reinforcement described by Dr Penman We agree that movement is not necessary, for we have observed reinforcement of the ankle-jerk produced by an effort to grasp when the forearm muscles were so paralysed by decamethonium that no detectable movement resulted We feel that the effort to move, whether accompanied by a movement or not, is the effective stimulus for reinforcement, and this is what we intended to imply in our paper

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A J BULLER
A C DORNHORST

TRICHOMONAS VAGINITIS

SIR,—Dr Marjorie Murrell (Dec 21) criticises our article on the action of 'Locan' pessaries in trichomonal vaginitis The following are her main points and our replies to them

1 That *our dosage of 'Penotrane'* was not that now recommended by the manufacturers The dosage used was the routine for the particular clinic and gave satisfactory results when the organism was sensitive The failure-rate was due to genuine resistance in the strains and agrees exactly with that found in other, earlier, trials and in general experience

2 That the exclusion of known promiscuous patients from the experimental series invalidates the comparison with the controls It was not possible retrospectively to discover whether the controls were promiscuous or not In any case the number of persons excluded from the trial was only five

3 That there is in her experience a higher rate of sensitisation than we report Her cases were treated elsewhere and when she saw them there was vulval eczema in 3 out of 12 The absence of eczema before treatment has not been established

In our cases, and apparently in Dr H C Perry's series (Dec 21), there was no evidence of sensitisation The case we mention complained of irritation but there was no inflammation or excoriation Sensitisation will occur in some patients but the frequency should be low The manufacturers of locan tell us that the same chemicals in other topical preparations are giving this in only 2 out of 15,000 cases treated

The remaining criticism of our paper is directed to the nature of the trial It appears to be widely believed that a mathematical estimate cannot be obtained unless alternate or randomly selected cases are treated and the remainder given blanks This is not true if, as in trichomonas infestation, there is little chance of spontaneous cure during the period of observation and if the cure-rate for the population at large under alternative treatment has been established over many years

The purpose of using a group of controls was to establish that the clinic population was not self-selected and notably atypical Since the figures for both preparations used agreed with earlier trials and with the accepted figures for failures in treatment, such a comparison was fair Using the familiar χ^2 technique, either with the series as published or with the addition of those cases still under treatment or in which the follow-up had been less than three months (giving 18 more cases with 3 relapses in previously relapsing patients, these now being taken as failures), the probability that the favourable results are due to a sampling error *is less than 0 001*

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H C STEWART

EFFECT OF *d*-TUBOCURARINE CHLORIDE ON BLOOD-PRESSURE OF ANÆSTHETISED PATIENTS

SIR,—As Dr Langton Hewer says in his interesting letter of Oct 26, there have been a number of reports of a rise of blood-pressure following the injection of *d*-tubocurarine chloride As far as I am aware, however, it has not been conclusively shown that such a rise can be attributed to the effects of this drug

The rises in my cases were mostly small—only three being greater than 10 mm Hg—and were not statistically significant The blood-pressure of the anæsthetised patient is not constant but varies in either direction for a variety of reasons, some of which are *ill* understood It was to this variability that I attributed the small rises in blood-pressure which I observed There is nothing in my results, therefore, to support the contention that *d*-tubocurarine chloride may raise the blood-pressure of some patients

I do not think that Dr Burchell's interesting remarks (Nov 9) are applicable to my results because control of respiration had been established in most of my patients at least 5 minutes, usually more, before the injection of *d*-tubocurarine chloride

University Hospital,
University of Saskatchewan,
Saskatoon, Canada

EDWARD T THOMAS

VALIDITY OF THE UREA METHOD FOR ESTIMATING TOTAL BODY-WATER IN MALNUTRITION

SIR,—Dr Srikantia and Dr Gopalan (Nov 23) recommend the use of urea for measuring total body-water There are a number of points to be remembered

A given dose of urea may not be completely absorbed, this may make calculations of total body-water inaccurate After administration of doses of the order of 100 g urea a day for the treatment of peptic ulcer, the blood-urea did not always increase as expected There were increased levels of urinary urea, but not to a sufficient degree, one could only assume an incomplete absorption of these relatively large doses My unpublished studies seem to confirm this view, but since unabsorbed urea may appear as fæcal ammonia rather than as urea, exact deduction is difficult

If urea is fully absorbed it must not be assumed that it will diffuse into all the body-water We have shown [1] that urea permeates slowly into the central nervous system

---

[1] Conway, E J; FitzGerald, O *J Physiol* 1942, 101, 86

Furthermore, some parts of the central nervous system may be impermeable to urea

Finally, it should be remembered that urea is not biologically inert Indeed, this is explicit in Dr Widdowson's suggestion, and the purpose of the paper by Dr Srikantia and Dr Gopalan was to assess its importance Urea may be broken down by gastric urease and by bacterial urease We have found that the amount of gastric ammonia after urea administration (orally or intravenously) might be quite great[2] This would affect the value of the urea as a test substance for total body-water These considerations (apart from the reference to the central nervous system) possibly apply only under somewhat unusual circumstances, such as where large amounts of urea are being used or where incipient renal failure is present They are, however, worth remembering

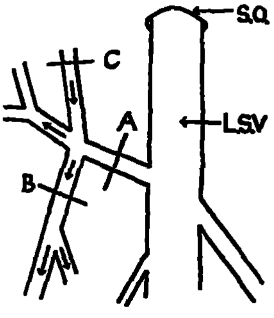
St Vincent's Hospital, Dublin,
and University College, Dublin

OLIVER FITZGERALD

THE STRIPPING OF VARICOSE VEINS

SIR,—Some of us have been performing this operation long enough now to come across an occasional recurrence When this is at the site of high resection or " top-tie", and the notes show that every single branch joining at that point has been resected, we have to ask ourselves why the bypass has occurred

I think the enclosed diagram may help to give us the answer in other words, resecting the joining branch *close* to the main trunk of the long (internal) saphenous vein may still allow a bypass through the distal branches To make quite sure that this state of affairs should not arise, it is necessary to resect and ligate at the points diagrammatically represented at C and B in the accompanying figure



Ligation of branches of long saphenous vein A site of usual ligation B, C: additional ligatures needed to prevent bypass L.S V: long saphenous vein S O saphenous opening

The most common cause of " recurrence " that comes my way I find to be failure to strip the short (external) saphenous vein when dealing with the eradication of the internal saphenous vein In a high percentage of cases this extra procedure I find to be necessary at the original operation

There are many other causes of recurrence, but I do feel that these two are of sufficient importance for our special attention

London, W 1

R ROWDEN FOOTE

A THYROID ASSOCIATION

SIR,—The Fourth International Goiter Conference is to be held in Britain in 1960 and the American Goiter Association, which usually holds its annual meeting in one of the cities of the U S A, is on this occasion holding its annual meeting in London in conjunction with the International Conference The London arrangements for these meetings are being made by a committee of the London " Thyroid Club "

These developments have raised the question of whether there should be formed a " Thyroid Association of Great Britain " or " of Europe ", which should probably be linked in some way to the Society for Endocrinology and the section of endocrinology in the Royal Society of Medicine If those who feel that some such association should be formed would notify the undersigned, the amount of support for this idea could be ascertained If it then seems desirable a preliminary meeting will be arranged, possibly in association with the national joint meeting of the Society for Endocrinology and the section of endocrinology in the Royal Society of Medicine

RUSSELL FRASER
SELWYN TAYLOR

Postgraduate Medical School, London, W 12

University Department of Medicine,
Gardiner Institute, Western Infirmary,
Glasgow

E J WAYNE

INTELLIGENCE OF DRIVERS

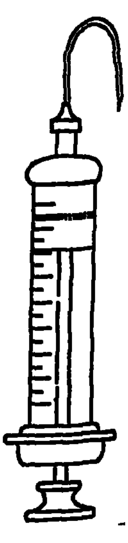
SIR,—Although I have not experienced the hazard described by Dr Millman (Jan 4) I have often thought that the sign " dual carriageway " itself offers a potential danger Neither " dual " nor " carriageway " is a word commonly used in speech and it is doubtful if the meaning of " dual " would be readily comprehended by the semi-literate The expression " dual carriageway " is liable also to be misinterpreted, for ordinary roads can be regarded as dual carriageways in the sense of providing two ways or directions of movement for vehicles Perhaps this is why the expression is not to be found in the Highway Code

Teddington,
Middlesex

A G J EVANS

AID FOR VOLUMETRIC FILLING OF SYRINGES

SIR,—Preparation of an accurately measured volume of fluid in a syringe is often associated with spilling and dribbling of the excess fluid as an attempt is made to get rid of air-bubbles This is especially troublesome when one is handling frothy fluid, such as blood, or radioactive material, where it is essential to avoid contamination



The problem can be solved by the simple means of using a U-shaped needle, shown in the accompanying figure This is prepared by bending an 18-gauge standard hypodermic needle, $2\frac{1}{2}$ in long, into the suitable shape, with careful manipulation the standard steel needle will take this strain without snapping, especially if first heated

The solution is drawn into the syringe beyond the graduation mark in the usual way, the U-needle is then fitted to the nozzle of the syringe which is held inverted When the piston of the syringe is pushed, all air bubbles are ejected, and excess fluid is returned to the stock bottle held in position below the needle-point During this manipulation sterile conditions can be maintained with ease

Department of Hæmatology,
Postgraduate Medical School of London,
London, W 12

S M LEWIS

ENZYME TESTS FOR GLUCOSE

SIR,—From time to time adverse reports have been published on the enzymatic testing of urine for glucose Recently Tunbridge[1] suggested an error of 11% when urine is tested in this manner On the other hand, the advantages of this method are such that it should not be rejected lightly unless there is clear evidence that it is unreliable

In my diabetic clinic at the Beverley Westwood Hospital, each patient brings with him four specimens of urine which have been passed at specified times on the previous day My present series covers 932 samples of urine each of which was tested by the ' Clinistix ' method and also by the standard

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[2] FitzGerald, O, Murphy, P *Irish J med Sci* 1950, March, p 97

[1] *Prescribers Notes,* 1957

Benedict technique in a water-bath The urine is tested by a laboratory technician Of those 932 samples 12 gave a false positive reaction On the other hand, not one gave a false negative. False positives are of little importance, as under normal routine all urines which give a positive reaction to 'Clinistix' must have this confirmed by water-bath test I strongly suspect that, in the case of at least some of the false positives, they were read off later than thirty seconds Those results would suggest that it is a reliable test for glucose in urine.

Beverley **R D MILLER**

INFANTILE GASTROENTERITIS

SIR,—I should like to support Professor Watkins' condemnation (Dec 21) of the indiscriminate use of antibiotics in infantile digestive disorders I use the latter term deliberately because I agree with Dr Easton (Dec 28) that most cases of so-called gastroenteritis seen nowadays are non-infective, rather do they result from dietetic mismanagement by the mother because of ignorance or indifferent professional advice

Present-day reliance on bottle-feeding leads to trouble at both the major weaning periods (1) when the mother first attempts to wean the infant from the breast on to the bottle, usually after leaving hospital, (2) when mixed feeding commences and choice of other natural foods becomes a problem At both times the divided responsibility of her advisers (hospital, child-welfare clinic, health visitor, midwife, and family doctor) does not favour unanimity of professional opinion, though it is true that the necessary explanation and reassurance is time-consuming The reason why babies do better in hospital is surely not the use of antibiotics, or a lessening of doubtful infectivity, but the skilled nursing (rather than medical) attention which is given to feeding, its timing, and above all the absence of panic and fussing

Ilford Isolation Hospital,
Romford, Essex **I M LIBRACH**

MANIPULATION FOR BACKACHE

SIR,—We must all applaud Mr Bremner (Jan 4) for drawing renewed attention to the useful part played by manipulation in the relief of backache This fact calls for reiteration until its value is recognised at every hospital in the country When this becomes so, patients requiring such treatment will no longer have their time wasted by futile physiotherapy nor be forced to go outside the N.H S to seek relief from lay manipulators

While I can only admire Mr Bremner's courage in manipulating under anæsthesia, this unfortunately militates against a good result. Comparison between his 10% complete relief after one session with the 57% reported by Barbor[1] and the 49% when anæsthesia is avoided,[2] shows clearly what a handicap anæsthesia is The reason is this

We are agreed that the aim is to restore a painless range of movement to the affected lumbar joint(s) But it often happens that forcing movement in one way does good whereas in another does harm Which technique is most suited to any one case can be discovered only by questioning the patient about his pain and assessing his range of straight-leg raising and of lumbar movements after each manœuvre Anæsthesia deprives the manipulator of this necessary guidance Moreover, the manipulation should cease when a painless range has been restored How can the manipulator know that this point has been reached unless the patient can stand up, move in each direction, and report the result? Good work carried out under adequate control demands a fresh assessment of the case after each separate manœuvre such as is rendered impossible by anæsthesia[3]

There is another disadvantage the small number of patients that can be treated if admission for the night, use of the theatre, and the services of an anæsthetist are needed Moreover, both hospital and patient are reluctant to repeat so elaborate a routine at whatever intervals prove necessary This is important, for relapse within three years amounts to over 40%, and some patients need treatment once or twice a year

We are careful to avoid physiotherapy after a successful manipulation, and regard it as useless when manipulation fails, hence our only after-treatment is postural instruction and perhaps a corset

Our statistical assistant, Mrs Granger-Taylor, has supplied us with the following figures for 370 patients, all seen in 1953 and followed-up for not less than three years

Pain in Back (46%)

(1) Treated by manipulation, 58%
  Well in one session, 49% } 60%
  Well in two sessions, 11% }
  Recurred within three years, 44% of those relieved by manipulation
(2) Treated by traction, 13%
  Well in two weeks, 38%
  Recurred within three years, 20%
(3) Treated by epidural injection, 17%
  Well, 43%
  Recurred within three years, 21%

Sciatica (54%)

(1) Treated by manipulation, 31%
  Well in one session, 33 5% } 45%
  Well in two sessions, 11·5% }
  Recurred within three years, 40%
(2) Treated by traction, 25%
  Well in two weeks, 68%
  Recurred within three years, 20%
(3) Treated by epidural injection, 26%
  Well, 66%
  Recurred within three years, 18%

These are personal figures At St Thomas's Hospital, as is well known, nearly all manipulation is carried out by physiotherapists It is thus probable that statistics based on their work would show results in rather more sessions, since many are still students However, these students have manipulated with success in cases where manipulation under anæsthesia had failed, hence I feel sure that Mr Bremner will be able to obtain results surpassing those in his present series, satisfactory though these already are, merely by avoiding anæsthesia

London, W 1 **JAMES CYRIAX**

SIR,—Mr Bremner's article is, I think, the clearest and least biased article on the subject that I have read

Being unprejudiced he inevitably arrives at the conclusion that manipulation is a good thing All right, let the manipulation be carefully applied and the manœuvres thoroughly studied, then, Sir, he can probably dispense with the anæsthetic and possibly eliminate one of the "variables"

London, W 1 **W HARGRAVE-WILSON**

EFFECTS OF CERTAIN PROTEIN FOODS ON BLOOD-SUGAR LEVELS AND GLUCOSE TOLERANCE

SIR,—When we reported our results[1] (Aug 17), we had also observed that two hyperglycæmic patients showed considerable improvement when their diet contained, in addition to their normal complement of rice or chappatis or bread, a greater proportion of fish, egg, or lean meat but little or no fatty food, such as bacon and pork However, as no quantitative data on the calorie intake of these patients had been recorded, it was thought that these observations could wait until we had occasion to publish in detail the results of our further study, now in progress, on the effects of ingesting different types of proteins (of both animal and vegetable origin) and their hydrolysates on blood-sugar and glucose-tolerance in healthy and hyperglycæmic subjects But in view of the interesting letter by Dr Bicknell[2] it seems appropriate to record our findings with animal-protein diets

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[1] Barbor, R. *Brit med J* 1955, i, 412.
[2] Cyriax, J Congress of Occupational Health, Helsinki 1957, vol. i, p 122.
[3] Cyriax, J Orthopædic Medicine, vol. i, p 454 London, 1957

[1] *Lancet*, 1957, ii, 317

Division of Biochemistry and Nutrition,
Central Food Technological Research Institute,
Mysore, India
M SRINIVASAN

OSTEITIS PUBIS AFTER INGUINAL HERNIORRHAPHY

SIR,—May I congratulate Mr Le Vay and Mr Borman on their report (Dec 21) I would like to add to their cases a personal one that occurred in a series of over five hundred herniæ in men over 50 years of age

The patient was a man of 50 and he evinced the same symptoms of backache and pubic and perineal pain Before the diagnosis was made he was seen by a rheumatologist, a physician, a neurologist, and my friend Mr E W Riches, who diagnosed the condition he was called in because of a suspicious hardness of the prostate (? carcinoma)

Although in this patient there was no apparent infection, I think the underlying cause is a subclinical infection about the stitch (in this case no 50 linen thread), which passes into the periosteum of the pubic tubercle, with a spreading reaction in the pubic vessels He completely recovered in 18 months His X-rays were identical with those shown by Le Vay and Borman It is a baffling and tiresome complication

London, W 1
HAROLD DODD

SIR,—Mr Le Vay and Mr Borman[3] should be congratulated on immediately recognising the condition of osteitis pubis as their "second and third post-herniorrhaphy patients tottered into the orthopædic clinic"

Osteitis pubis was first described as a postoperative complication by Legueu and Rochet in 1923[4] and fully dealt with by Edwin Beer[5] [6] in 1924 and 1928 Many papers have appeared on osteitis pubis since, but not very much has been added to Beer's original postulate that most probably trauma and infection were the main factors responsible for the development of this complication

I drew attention to this condition in 1947[7] after I had diagnosed osteitis pubis in one of my patients, who was shown at the meeting of the Middlesex County Medical Society on June 9, 1945 Although not generally known then, the syndrome later did become well recognised in the British Isles, especially among urologists, as a complication following operations on the bladder and prostate As I observed in 1947, typical instances of osteitis pubis had already been reported following operations for hernia and further observations would prove that this complication was not rare

It was interesting to read again about the failure to influence the course of this condition by any active treatment including cortisone I have had the opportunity of trying cortisone and found that it did relieve the pain (previously quite unaffected by large doses of morphine) and allowed the patient free movement, but the injections had to be discontinued on account of prohibitive side-effects

In my own personal series of 300 suprapubic bladder operations, chiefly prostatectomies, on which I reported in 1947, osteitis pubis arose in 10 patients (3%) Looking back, I now believe that this was most probably due to a flaw in my technique, as all lower abdominal operations infringing the integrity of the pubic periosteum would appear to be liable to the complication of osteitis pubis

London, W 1
E KIRZ

RADIATION FURTHER WARNINGS

SIR,—The leading articles and annotations of *The Lancet* used to be, and should still be, like Cæsar's wife It is true they are difficult to write They review data published in the world's scientific and medical press and often give guidance to the reader in the form of critical editorial opinion The journal and its editors cannot be blamed for drawing the "wrong" conclusion or holding "wrong" opinions, but they can be castigated for misreporting the data

Recently I have been taken to task by my colleagues overseas for permitting to pass without comment a leading article in *The Lancet* referring to radiobiological work in which the data were wrongly reported It was left to workers in the Netherlands to voice objection in a letter to *The Lancet* Unhappily there is now a recurrence in the annotation of Dec 28 I must beg leave to point out the error

After summarising some recent publications, in fair but somewhat lurid form, the annotation works round to genetic damage produced by radiation, it then becomes misleading To Glass[1] is attributed the statement "Since mutations are caused by the fracture of a chromosome followed by reunion of the broken ends in a new pattern, at least two fractures are needed for a mutation, that is why the incidence of mutations increases as the square (or some higher power) of the dose" In fact Glass was very careful to discriminate between *chromosomal* mutations such as the above and *point* mutations I quote from his article

> "Inasmuch as the chromosomal mutations are produced chiefly by high doses, and in those very cells that are most readily eliminated through the production of the well-known temporary sterilisation of the male after acute doses of radiation, there is relatively little genetic damage to be expected from them
>
> "Of chief importance, then, are the point mutations, in which the lesions of the hereditary material are submicroscopic in size
>
> "All existing genetic evidence indicates that the frequency of point mutations increases linearly with the radiation dosage"

Everything that I have quoted from Glass is standard teaching based on scientific data It has all been said many times before and is to be found in the report of the Medical Research Council's committee[2] and in the report of the National Academy of Sciences[3] It is true that Glass interprets the established data in a rather more pessimistic fashion than either of the national committees, like any thinking scientist, he is fully entitled to his personal opinion It is not right, however, for you to take Glass' opinions and hang them on to distortion of the facts

Radiobiological Research Unit,
Harwell, Berks
JOHN F LOUTIT,
Director

CHEST X-RAY EXAMINATIONS AND RADIATION HAZARDS

SIR,—Dr Anderson, from his letter in your issue of Jan 4, does not seem to realise that his camel has now shrunk as a result of the advent of long-term chemotherapy until it is small enough to pass through the eye of a needle

The Chest Clinic,
Harrow, Middlesex
R GRENVILLE-MATHERS

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[2] *Lancet*, 1957, ii, 388
[3] Le Vay, D , Borman, J B *Lancet*, 1957, ii, 1252
[4] *J Urol, med chir* 1923, 15, 1
[5] Beer, E *Int J Med* 1924, May, vol 37, fasc. 5
[6] Beer, E. *J Urol* 1928, 20, 233
[7] Kirz, E. *Brit J Surg* 1947, 34, 272

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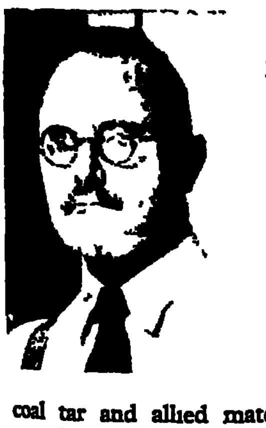
[1] Glass, B *Science*, 1957, 126, 241
[2] The Hazards to Man of Nuclear and Allied Radiation Cmd 9780 H M Stationery Office, 1956
[3] National Academy of Sciences and National Research Council, The Biological Effects of Atomic Radiations Washington, 1956

Obituary

ERNEST LAURENCE KENNAWAY

Kt, M.A, D M Oxon, D Sc Lond, F R C.P, F R S

Sir Ernest Kennaway, who died on Jan 1 at the age of 76, had the great gift of scientific curiosity in such degree that neither disabling illness nor age could turn him from his purposes The achievements of his able mind included the first demonstration, in 1930, that cancer can be produced by a pure chemical compound, and through many years he proved a leader in the new study of carcinogenesis



Son of L J Kennaway of Exeter, he distinguished himself as student and graduate successively at University College, London, at New College, Oxford, at the Middlesex Hospital, and at Guy's Hospital, where for some years he demonstrated physiology From the first he was interested chiefly in the biochemical side of medicine, and he did much work on purine metabolism and on acetonuria From Guy's he moved back to The Middlesex as chemical pathologist, and thence to the Cancer Hospital Already in the early 1920s he recognised that the cancer-producing properties of coal tar and allied materials implied the presence of specific chemical individuals having this property, and he undertook a series of painstaking researches, unaided except by a technician whom he trained, in which he examined tar fractions and a large number of the known constituents of tar

From his first paper, published in 1924, an important conclusion was that the cancer-producing substance was present in a fraction of pitch distillate which came over above 500 C This work was followed by studies of artificial cancer-producing tars formed by the pyrolysis of acetylene, isoprene, cholesterol, and other organic materials, and then of the very potent high-boiling fractions of the mixture of hydrocarbons formed by the action of aluminium chloride on tetrahydronaphthalene Although Kennaway himself seemed not to appreciate the fact, this pioneer work showed fairly conclusively that the materials he sought were complex hydrocarbons, probably of aromatic type

These efforts were presently supplemented by those of physicists, chemists, and a biochemist in the team which he assembled, and had their culmination in 1932 in the isolation from coal-tar pitch of a potent carcinogenic hydrocarbon which was shown by synthesis to be the hitherto unknown 3 4-benzpyrene Kennaway's own general account of these researches was published in 1955 A parallel line of investigation, based on the fluorescence spectroscopic studies of Mayneord and Hieger, led to recognition of a considerable group of potent carcinogenic hydrocarbons, all of them prepared synthetically The carcinogenic activity of the first of these, 1 2 5 5-dibenzanthracene, was described by Kennaway in 1930, although, through a chemical error which Dr J W Cook was able to correct, the compound was wrongly described in his paper as 1 2 7 8-dibenzanthracene

A detailed account of the biological properties of these hydrocarbons is given in a series of papers in the *Proceedings of the Royal Society* with the general title of the Production of Cancer by Pure Hydrocarbons A brief summary of these and later developments by Dr Cook appeared in our columns last February

Perhaps equally important were Kennaway's epidemiological studies, carried out with Lady Kennaway, who also assisted in his experimental researches

This very laborious work involved the examination of tens of thousands of death certificates and illustrates Kennaway's flair for amassing, classifying, and correlating data Such studies have aimed at correlating the numbers of deaths from cancer, in various years, with sites of the disease and occupations, environments, and other circumstances of the victims The Kennaways' 1936 publication, a Study of the Incidence of Cancer of the Lung and the Larynx, was one of the earliest papers to focus attention on the rising incidence of lung cancer, especially in men It was followed by two others in the same field, in 1947 and 1951, and in the latter year Kennaway also published an illuminating survey, Cancer of the Lung in Relation to Tobacco, in which he followed up an earlier experimental study of the arsenic content of tobacco from various sources

Of the man who achieved this big output of valuable work, some idea is given by the following extracts from tributes by his friends

* * *

Sir Ernest Kennaway was one of the great men of his generation He was essentially a shy man and in some respects unduly modest He shunned publicity and was perhaps little known outside the immediate circle of his medical and scientific colleagues Until his latter years he declined to take part in public discussion in any form, even at small intimate scientific gatherings This was probably due in part to the handicap of the affliction from which he suffered for more than thirty years, but which he was able largely to overcome by dogged determination and sheer force of character He was a man of high principles and would pursue any course in which he believed with the ardent zeal of a crusader He would never take " no " for an answer, and compromise was no part of his make-up None, however eminent or exalted, were spared the lash of his tongue or the pungency of his pen when he disapproved of their actions or their neglect to act Himself very painstaking and methodical, he had no patience with careless or slipshod work in any form, and was quick to point out inaccuracies and to rebuke their authors One of his last remarks to me, a month before his death, was " Well, although I can no longer walk, I can still bite "

But the picture of a stern, forbidding personality would be unjust to his memory Although Kennaway was not a man with whom people took liberties, he was nevertheless a friendly and hospitable man, and in the manifestation of these qualities he was greatly helped by the grace and charm of Lady Kennaway, to whose care and support he owed much In his own way he had a keen sense of humour He was particularly kind and generous to his younger colleagues, many of whom had good cause to be very grateful to him for his inspiring encouragement and for the stimulating enthusiasm with which he took an interest in their work He displayed unbounded confidence in their ability to overcome their difficulties and great delight when they succeeded

Sir Ernest was no narrow specialist He had received a broad scientific training in addition to his medical training and was also a man of wide general culture In his latter years he took some interest in religious beliefs and religious customs, but his views were rather bigoted and this was not one of his happiest pursuits He had a graphic style and his published accounts of his travels—to Iceland, to Norway, and to the United States, for example—were full of factual information of great value and punctuated with entertaining asides and comments on details which would have escaped the notice of most people At one time he was interested in the cinema, and his article, Zadigism and the Cinema, published in *St Bartholomew's Hospital Journal* in 1949, is an amusing commentary, which shows some of his breadth of knowledge, on the incongruities as regards both time and environment of some of the films he had seen

For about forty years Kennaway had dedicated himself to cancer research, and no-one has made greater contributions to it than he This has been generally acknowledged throughout the world His work is characterised not only by the genius which comes of an infinite capacity for taking pains but also by an inspired faith in its methods and its outcome That he was able to make the right approach was due in no small measure to his detailed knowledge of various fields of pathology, chemistry, and biochemistry His general appreciation of several branches of science enabled him to guide and direct the efforts of a team of experts, each of whom was enabled to bring his own specialised knowledge and experience to bear on the problems under investigation

Though it is probably too early to make a final assessment of the importance of this work, it has completely reorientated cancer research Kennaway himself wrote of it in 1945 with characteristic understatement "The very numerous carcinogenic compounds which have been discovered in the last 15 years have served, even if they have done nothing else, to dispel some of the rather hopeless mystery which used to surround the whole subject of the ætiology of cancer" It is to be hoped that a collection of his more important papers may yet be reprinted They would serve as models for many young people embarking on a research career J W C

Others, who knew Sir Ernest earlier than I, will describe his pioneer work, which all respect and which many of us would do well to reread at intervals I met him first during the last war, when on the eve of enlistment I came to ask him whether a bit of unfinished work was worth recording he made me publish it Later I found myself on the fringe of his wide zone of interest in tobacco carcinogenesis, and undertook some tests in this field He had a remarkable way of showing his interest in one's work, which often seemed to give it an importance one had not thought it possessed I feel an affectionate gratitude for the kindly and persistent efforts he made, despite illness, during recent years to stimulate and encourage and guide those whom he believed could help in the study of lung cancer M H S

During the last years of his life Sir Ernest suffered from at least four major conditions, any one of which would have been sufficient to induce most other men to cease active work But though his body was infirm his mind retained an extraordinary vigour It was characteristic that during his last illness, when he knew that he was seriously ill, he wrote an article on nursing from the patient's point of view, and continued to plan for the future, only two days before his death he telephoned a friend to inquire about the chemical peculiarities of the fuel used to smoke fish in Iceland, which process he thought might contribute to the high incidence of cancer of the stomach there

In later years his interest centred particularly on the epidemiological approach to the study of cancer, and he published papers on the epidemiology of cancer of the larynx, lung, penis, and cervix uteri But he was never content merely to discover differences in incidence, his object was always to find out what lay behind them and how they were produced No aspect of human behaviour was too trivial for his attention, and he allowed no taboos to stand in his way Any subject was fit for speculation, but he distinguished himself from so many others by immediately setting out to obtain quantitative data which would allow his speculations to be tested

He was not an easy man to get on with and took offence at times, where none was intended This, however, nearly always arose because of his inability to appreciate how much he was honoured He was in reality a humble man and always assumed that his contributions and opinions were unwanted and would be ignored He was at his best in contact with young workers, whom he treated as his equals, and he was as ready to learn from them as they were from him To those who worked along with him he showed a lively sense of humour and a warm humanity, to them he was a source of constant inspiration and a model of the devoted inquirer after truth

R D

HAROLD GEORGE BEDFORD RUSSELL

M.A , B Chir Cantab , F R C S

Mr H G Bedford Russell, consulting surgeon to the ear, nose, and throat department of St Bartholomew's Hospital, London, died on Dec 30 at his home in Oxfordshire

He was born at Geelong, Victoria, in 1886 and went to school in Australia He came to this country to study medicine at Sidney Sussex College, Cambridge, and at St Bartholomew's Hospital, qualifying in 1911 During the 1914–18 war he served in France with the rank of major, and acted as D A D M S of IX Corps For his work he was mentioned in despatches and awarded the Croix de Guerre

In 1919, after he was demobilised, he took the F R C S and was appointed chief assistant to the ear department at Barts under Ernest West and Sydney Scott After West's retirement the departments were regrouped and Bedford Russell moved to the throat department, then a separate unit under Mr Douglas Harmer and Frank Rose Bedford Russell was closely associated with Mr Harmer in his assessment of the value of radiotherapy in cancer of the upper air-passages (later published as the Semon lecture of 1931) Much of the analysis of results and data was entrusted to Russell

Russell also joined the staff of the Hospital for Diseases of the Throat in Golden Square, at first as registrar, later becoming assistant surgeon, surgeon, and dean He worked for some years at the Facial Injuries Hospital at Sidcup at the time when Sir Harold Gillies and Prof Pomfret Kilner were laying the foundations of modern plastic surgery In 1928 he was appointed assistant surgeon to the throat department at Barts, and two years later he succeeded Frank Rose as head of the department

Bedford Russell worked extremely hard at his hospitals, quickly built up a large private practice, and yet was an active member of a number of medical societies From 1932 to 1934 he was secretary of the section of laryngology of the Royal Society of Medicine, and he arranged for Ferris Smith to visit this country and demonstrate to his colleagues here his external operation for chronic ethmoiditis

Of Bedford Russell's work as a surgeon and his interests as a man F C O writes

Bedford Russell was enterprising and energetic in everything he did In his professional life his early efforts were concentrated on the throat, but later his attention became diverted to the paranasal sinuses He took up the study of infection of the sinuses with customary zeal and developed the operative technique to the most complete drainage and exenteration possible He became interested in the effect of sinus infection on the mind and gave many years to the study and investigation of the relation between sinus disease and mental disorders He was associated with a number of institutions and societies concerned with mental diseases and wrote many papers on the subject

He was a keen tennis-player, putting his characteristic dynamic energy into the game and deriving equally characteristic enjoyment from it He took up skiing with the same enthusiasm, visited Murren every year, and gave the Bedford Russell cup for which an annual competition is held He derived the greatest exhilaration from the weeks he spent each year in Switzerland He took to country life, with its attendant sports and responsibilities, with the usual energy and drive and rented and farmed a number of estates in various parts of the

Home Counties The part of squire was one that afforded him great satisfaction.

Mr Bedford Russell married in 1928 Lilian, daughter of the late Harold Longmore-Mavius She survives him with their two sons

HAROLD PERCY WALLER BARROW

C.B., C.M.G., D.S.O., O.B.E., M.R.C.S., D.P.H., D.T.M.

Major-General Barrow, who died on Dec. 20 at the age of 81, was director of hygiene at the War Office from 1924 till 1930 and colonel commandant of the Royal Army Medical Corps from 1941 to 1946

He was born at Madras, the son of Colonel H J Waller Barrow, A.M.S After qualifying from Guy's Hospital in 1898 he became a surgeon probationer, and he received his commission in the R.A.M.C. the following year. He served in South Africa from 1900 to 1902 and later he was posted to the Punjab and to Jamaica. In the first world war, after a time as deputy assistant director-general at the War Office, he served in France as A.D.M.S of a division and was awarded the D.S.O in 1918 After the war he returned to India as deputy director of hygiene and pathology at Army Headquarters, and in 1924 he took up his last Army appointment as director of hygiene at the War Office.

After he retired in 1930 he became health officer in Antigua and a member of the Federal Executive Council of the Leeward Islands and Antigua until 1933 Later he settled at Epsom where his many activities included work as a commissioner of the Royal Hospital, Chelsea, and as a member of the committee of the Royal Patriotic Fund Corporation. Some years ago he moved to Brockenhurst, and he died at his home there. In 1901 he had married Miss Estella Hertog of The Hague, by whom he had two sons and a daughter

A colleague writes that many who as young officers served under Boy Barrow will remember "his kindly interest and the hospitality which he and his wife dispensed so generously and so enjoyably."

WILLIAM JAMES FENTON

M.D. Camb., F.R.C.P

Dr Fenton, consulting physician to the Brompton Hospital and Charing Cross Hospital, died in London on Dec. 24 at the age of 88

He was educated at Leamington College School, Caius College, Cambridge, and St. George's Hospital. After qualifying in 1894 he held several resident appointments at St. George's, and he seemed set for a place on its staff. But he was unlucky, for, when he reached the age when promotion could be expected, no vacancy seemed likely for some time. Fenton accordingly applied for and obtained an appointment at Charing Cross Hospital as an assistant physician. Shortly afterwards a death vacancy occurred at St. George's, but Fenton felt that as he had thrown in his lot with Charing Cross he could not seek election to St. George's, though it was a great disappointment. Soon afterwards he was elected to the staff of the Brompton Hospital, and he became a fellow of the Royal College of Physicians in 1907.

The National Health Insurance Act of 1911 called for the setting up of a tuberculosis dispensary for Chelsea, and when it was decided that this should be located at Brompton, Fenton became medical officer in charge. For some years he was dean of Charing Cross Hospital Medical School, and later he became dean of the Brompton Hospital School. He retired from the staff at Charing Cross in 1933, and remained till 1939 at Brompton, where a member of the staff at that time need not retire until he had been a full physician for twenty years

Fenton was one of those who was a consultant in diseases of the chest before chest X-rays had shown their worth; but he was quick to appreciate their value as soon as technical advances produced satisfactory plates, and in *Diseases of the Chest* (1930) with his co-author, the late L. S. T. Burrell, he suggested that the importance of clinical signs could be exaggerated in view of the precision of modern methods of diagnosis. Of Fenton as a colleague and a friend, F. H. Y. writes

He was a capable and careful physician, though his was not an original mind. His work at his hospitals was of a high standard, and he was popular with his patients because of his interest in their welfare. His chief hobby was photography, and after his retirement he presented to the Brompton Hospital Medical School two volumes of beautifully reproduced photographs of X-rays of obscure diseases of the chest. Architectural photography was another of his interests when on holiday In the early part of the war most of his time was spent taking photographs for the National Buildings Records He was keenly interested in music, and as a young man was a competent performer on the violin. Fenton was not easy to get to know, and few of his colleagues knew him except through his hospital work. Those who did know him, however, found a kindly and perceptive man.

Dr Fenton's wife died in 1930, and one of his sons was killed on active service during the late war. He is survived by a daughter and a second son.

EDITH MAY HALL

M.D. Lond., F.R.C.S., F.R.C.O.G

Miss Edith Hall, gynaecologist and obstetrician to the South London Hospital for Women, died at her home in Hampstead on Dec. 26 at the age of 61.

She graduated M.B. from the London School of Medicine for Women in 1920, and on taking the M.D. in 1922 won the university gold medal in midwifery and gynaecology. In 1923 she was appointed an assistant in the obstetrical and gynaecological unit at the Royal Free Hospital.

She also joined the staffs of the Marie Curie Hospital when it was first opened in 1925, and of the London Homoeopathic Hospital. In 1935 she became assistant surgeon, and later full surgeon, to the South London Hospital for Women. For many years she also held the post of consultant gynaecologist and obstetrician to the London County Council hospitals service.

Since 1949 ill health had gradually forced her to give up much of her hospital work, but she remained on the staffs of the London Homoeopathic Hospital and the Marie Curie Hospital until her death. How much she still found time for is shown by the following tribute from O R.

Edith Hall's success was due to natural ability, combined with a phenomenal capacity for sheer hard work, and a retentive memory. She also developed at an early age the maturity of mind and character and the sense of responsibility which made her such a valuable member of her profession. She never had a great fund of physical energy, although she was able to stand for long hours in the operating-theatre. Her hospital appointments entailed many regular sessions and a considerable amount of emergency work. She had long distances to cover by car, and always drove herself, and any time left over must have been fully occupied with committees and with her private patients. Despite all these demands she never allowed herself to be hurried over her professional work; she was in fact a slow worker, spending a considerable time in talking to her patients and allowing them to talk to her, thus making an effort to get to the bottom of their difficulties and troubles. She had an exceptionally amiable temperament, always appeared calm and unruffled. Completely [illegible] her innate charm and courtesy of manner never [illegible] always sincere. She had a sense of humour, and an [illegible] character, even when she [illegible] herself, her standards were high and she never [illegible] what she considered right Her judgment of people could be penetrating and acute, though she looked on the failings of others with a slightly humorous and kindly tolerance, and she never spoke unkindly about anyone

Though she had considerable strength of character and held decided opinions, she was always conciliatory, and on those occasions when she felt very strongly about anything, especially where the running of the hospital or the welfare of the patients was concerned, she could be tenacious to the point of obstinacy, nevertheless she always listened with courtesy to the views of others, and often managed to get what she wanted by tactful persuasion

In spite of her busy life, she always found time to keep in touch with her old house-surgeons and registrars, and she took a great interest in their careers Many of them are now settled abroad, and they always found a welcome at her house when they came back to London She had little time for hobbies, but was interested in archæology and architecture, and spent many of her holidays travelling abroad with her sister It is sad that her death should have come as she was looking forward to a peaceful retirement, with the opportunity for doing all those things for which she had never before had time

THOMAS HERBERT CECIL BENIANS

F R C S

Mr T H C Benians, honorary consulting pathologist to the Prince of Wales's General Hospital and to the Tottenham Group of Hospitals, died on Jan 1 at the age of 75

For a short time after qualifying from the London Hospital in 1907 he worked in South Africa and Rhodesia In 1914 he was appointed pathologist to the Prince of Wales's General Hospital and later he also became part-time pathologist at the North Middlesex Hospital, where during the late war he did much to build up the blood-transfusion service Soon after the war he gave up this post to become whole-time pathologist to the Prince of Wales's General Hospital and, within a short time, to the Tottenham Hospital Group under the National Health Service After he retired in 1951, he continued to work sometimes as a locum at other hospitals, and when not thus engaged continued his own research in his old laboratory at the Prince of Wales's General Hospital, where he was working until a few months ago

The North London Postgraduate Medical Institute owes much to the work which Benians put into the old North East London Postgraduate Medical College, of which he was for many years the vice-dean He was responsible for drawing the North Middlesex Hospital, and later Chase Farm Hospital, into the scheme, and on this amalgamation the present institute was founded The pathological museums of the institute are formed around the nucleus that was collected by Benians and his staff

Of his position and friendships at the hospital B H J writes

Tommy Benians was a popular figure at the Prince of Wales's General Hospital, and generations of housemen came to regard him as a father confessor who would give sound advice on pathology and on many other matters not necessarily related to professional work Such phrases as "You surprise me", "Now that's interesting", and "You must tell me more" when associated with a merry twinkle from his blue eyes encouraged the most bashful young man and conversation would flow freely Over lunch he would often recount little incidents with great enjoyment, but never with malice and never in a manner to cause any hurt He never claimed to be a clinician, but his advice on further investigations that might prove fruitful was often sought and often solved a clinical problem On one occasion he listened to a junior house-physician's account of a patient brought to the casualty department who died almost within minutes, and Tommy said, "Now that's interesting you will find that he has a rupture of the aorta into the pericardium", and the autopsy proved the correctness of his diagnosis

Gardening and growing flowers gave him great pleasure, and when he lived in a flat during his latter years his small allotment was a continual joy to him He was also a keen amateur artist, and of this interest P H M-B relates

In recent years I knew Benians more through his paintings than through his work He was a member of the Medical Art Society and besides attending our evening sessions he exhibited from time to time some of his original and quizzical compositions It was always good to meet him, for he possessed an unusual and refreshing turn of mind, and he preserved the same lively interest and whimsical turn of humour as in our student days at the London Hospital

Mr Benians leaves a widow, two sons, and a daughter

JOSEPH LENNOX PAWAN

M B E, M B Edin, D P H

Dr Pawan, formerly bacteriologist and pathologist to the Government of Trinidad and Tobago, died at his home at Port of Spain on Nov 3 at the age of 70

He graduated M B from the University of Edinburgh in 1912, and after postgraduate work at the Pasteur Institute, Paris, and in Germany, he returned to the West Indies and took up the appointment of Government bacteriologist which he held for over a quarter of a century He published papers on serum-calcium levels, pulmonary tuberculosis, sleeping-sickness, and the bacteriology of water-supplies and food-poisoning in the tropics, but his most important study was his articles on the transmission of paralytic rabies by the vampire bat, and he was appointed M B E for his investigations into the pathology and histology of this disease In 1954, he visited America as a consultant on rabies to the United States Government He was invited to become joint chairman of the Rabies Committee of the World Health Organisation, but ill health forced him to decline this invitation He is survived by his widow, one son, and two daughters

Sir THOMAS DUNHILL

A P B writes

Thomas Dunhill was a brilliant surgeon and essentially kind, two attributes not always met with together The two most beautiful sights I have witnessed in surgery were the late Lord Moynihan operating in the abdomen and Sir Thomas on the exophthalmic thyroid There was no fluster, the silence was broken by the click of the forceps, though the former might discuss the latest novel Each was gentleness personified Lord Moynihan used to teach "Every pull is a pain" But the most impressive feature was the absence of blood despite the vascularity of the organs

Appointments

GRIFFITH, D H S, L.R C P E, D P H, D I H M O H, Guisborough, Loftus, Skelton, and Brotton, Yorkshire

SACKWOOD, MARK, M B Lond, D OBST senior assistant M O H (maternal and child welfare), Middlesbrough

SHEPHARD, R H, M D Lond, F R C.S part-time consultant neurosurgeon, Derby group of hospitals

Births, Marriages, and Deaths

BIRTHS

DAY—On Jan 3, to Sonia, wife of Dr F M Day—a daughter, a sister for Carolyn

DEATHS

BENIANS—On Jan 1, at the Prince of Wales's General Hospital, London, N 15, Thomas Herbert Cecil Benians, F R C.S, aged 75

Notes and News

NEW LOOK FOR LAMBETH

"WHEN Hitler has finished bombing our cities," wrote Herbert Read during the war, "let the demolition squads complete the good work" The squads will soon be at work again on the south bank of the Thames, for the governors of St. Thomas' Hospital are planning their share of the reconstruction. The hospital was badly hit by bombing, by the end of the war seven of its thirty wards were destroyed and fourteen unusable, and it has lately been found that the buildings remaining are so unsound that they are not worth renovating The board have a plan which entails the diversion of Lambeth Palace Road further from the river, thus doubling the area of the hospital site They have provided a block of flats, now nearing completion, to house those whose homes will be demolished

A completely new building is to be erected, in stages to enable the present hospital to function during the building The main block of the new hospital, 120 yards from the river, will be 11 storeys high, containing 32 wards (827 beds) in 8 storeys, a 4-storey building, connected to it and lying between the main block and the road, will house outpatient departments and operating-theatres Other buildings, some of them in the space between the main block and the river, will provide accommodation for nurses, residents, and students, and (it is hoped) house the medical school The main block will be about 140 feet high, and the buildings nearer the river about 80 feet—the height of the present structure Most of the space between wards and river will be open, allowing excellent views The construction will be of concrete, but details of finish are not yet decided. Communication will be vertical by means of 4 towers housing lifts and stairs, the fifth and eighth floors (which will house laboratories) and the ground floor will provide horizontal communication The wards are designed in accordance with principles enunciated by the Nuffield Provincial Hospitals Trust, each will have a central entrance and service rooms

The Minister of Health has provisionally approved the scheme, subject to agreement on the scale of residential accommodation, it is being submitted to the Royal Fine Arts Commission and to the London County Council (the planning authority) Each of the four stages of building is estimated to take about 2$^1/_2$ years, and the total cost of the hospital (excluding the medical school and the road diversion) is put at about £7$^1/_2$ million It is hoped that building may begin some time next year

TELEVISION PROGRAMME ON CANCER

CANCER research was the subject of a recent B B C television programme An anonymous surgeon, who admitted to eradicating rather than curing cancer, introduced several research-workers Prof J F Danielli dealt with the question "what is cancer?" and showed cinemicrographic films of normal and cancerous cells dividing Dr R J C Harris described carcinogens, and Prof Geoffrey Hadfield discussed the role of endocrines in breast malignancy Dr L H Gray showed a film of dividing cells, revealing clearly the influence of radiation on the chromosomes Finally, methods were shown of testing chemicals that arrest malignant growth Summing up, the chairman emphasised that though no cure had been discovered, research was continuing along several lines, and the final answer might come from any of them

The symposium gave a good impression of the vigorous approach to the problem by several routes, and conveyed well the feeling that the chances of finding a cure were hopeful rather than encouraging at present There was no attempt to talk down to the audience and the excellent animated diagrams and film clearly illustrated the points being explained The random use of the terms "cancer", "carcinoma", and "malignancy" may have been confusing to some viewers The production (by James McCloy) was carefully planned and well presented

CARE OF DRUG ADDICTS

A STUDY group of the World Health Organisation has issued a report[1] on drug addiction It is concerned solely with addiction to opium (and its derivatives and synthetic substitutes) and to cannabis derivatives It deals with treatment, and considers prevention only as regards relapses

Addicts are classified according to their amenability to treatment Easiest to treat (often by mass methods) are those who fall into addiction during some temporary stress—e g, hunger, a painful illness, or the depressive phase of cyclothymia Harder to treat successfully are those with a basically pathological personality There is usually immaturity of character development and a desire to live only in the present or a destructive or self-destructive tendency, besides a lack of capacity for dealing with stress The causes may be found in emotional deprivation, lack of a parental figure to form a proper ideal (both common in broken homes), or over-indulgence during childhood, or an unrealistic attitude with standards differing from those of the patient's basic subculture Patients may, however, move from group to group

The fundamental need in treatment is effective control of the drugs concerned The addict must be regarded as a patient For those who do not respond easily to simple or mass methods, treatment will be psychotherapeutic and not essentially different from psychotherapy in other personality disorders It should aim at giving the patient more insight, understanding of the unreal character of his neurotic fears, and a better judgment of situations Maintenance of addiction is not treatment and should be reserved for special circumstances, withdrawal is important though only a part of treatment It is distressing and must be done with skill, speed, and humanity, and must be fully discussed with the patient It may be gradual or abrupt, supportive treatment, with sedatives and perhaps intravenous infusions, may be given, and in some cases electric or insulin shock therapy The methadone substitution technique[2] is recommended, but sedatives and tranquillisers "often make the withdrawal unnecessarily dangerous"

The continued-treatment stage, which aims at reablement of the patient till he can withstand the normal stress of life without using drugs, is time-consuming but the most important Withdrawal may be so unrewarding that the patient fails to continue treatment, or may lead to overconfidence Over two or three years the relapse-rate is high, and the patient needs support from his physician and friends and from social agencies The most effective method in most countries is civil commitment to medical care, with a gradual return to society through open wards and halfway houses

The report ends by calling for further studies of the prevalence of addiction in various countries, for diagnostic tools such as a urine test for the drugs concerned, and for extensive life-histories of addicts Annexes consider the ætiology of addiction and the legal framework of treatment in various countries

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Whitley Dispute

On Jan 2 representatives of administrative and clerical workers in the National Health Service decided to end the ban on overtime which began on Nov 18 as a protest against the Minister of Health's refusal to approve a 3% pay increase recommended by the Whitley Council for these workers (*Times*, Jan 3) A fresh claim for a 5% increase is being submitted to the council, if the management side reject this claim, it could then be referred to arbitration by the Industrial court

Royal Society of Health

On Wednesday, Jan 15, at 2 30 P M at 90, Buckingham Palace Road, London, S W 1, Dr W S C Copeman, chairman of the Empire Rheumatism Council, will speak on the problem of rheumatic diseases

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[1] Treatment and Care of Drug Addicts Report of a Study Group *Wld Hlth Org tech Rep Ser* no 131 World Health Organisation Geneva 1957 Pp 19 1s 9d

[2] Vogel V H, Isbell H, Chapman K W *J Amer med Ass* 138 1019

British Association of Allergists

The annual general meeting of this association will be held at 11 A M on Saturday, Jan 18 at 1, Wimpole Street, London, W 1

Canadian Poliomyelitis Vaccine

The first consignment of Canadian Salk vaccine arrived by air in Manchester last Saturday, on its way to the Liverpool headquarters of Evans Medical Supplies, who are handling the vaccine in this country (*Times*, Jan 6) This batch contains four tons, and altogether 5 million doses have been ordered

Laboratory Animals Bureau Congress

Sir Solly Zuckerman will open this two-day congress at 9 30 A M on Monday, March 24, at the Medical School of the University of Birmingham Further particulars may be had from the bureau, M R C Laboratories, Holly Hill, Hampstead, London, N W 3

Anglo-French Exchange Bursaries

Short-term grants for work in France are offered again this year to British doctors and medical research workers by the Institut National d'Hygiène, Paris Application forms can be had from Dr G W Wolstenholme, Ciba Foundation, 41, Portland Place, London, W 1 The closing date for application is Feb 2

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold public hearings on Thursday and Friday, Jan 16 and 17, at 11 15 A M, at Church House, Great Smith Street, London, S W 1 Representatives of the Medical Practitioners' Union have been invited to attend on Jan 16, and Lord Moran has been invited to attend on Jan 17

Conference on Work Study

This conference, convened by the British Institute of Management, will be held in Caxton Hall, London, S W 1, on Feb 6

The programme will include a talk by Mr R P MacMahon, deputy house-governor of the Westminster Hospital, on work study and the hospital service Full particulars may be had from the press officer, Management House, 80, Fetter Lane, E C 4

The Royal Society

Sir Lindor Brown and Sir Charles Dodds have been appointed vice-presidents of the society for 1957–58

Awards under the Society and the Nuffield Foundation Commonwealth bursaries scheme have been made to Dr A J Buller, senior lecturer in physiology, St Thomas's Hospital Medical School, London, and Dr W P U Jackson, senior lecturer in medicine, University of Cape Town

Roehampton Courses on Artificial Limbs

Courses on artificial limbs and rehabilitation after amputation, for consultants and senior registrars in orthopædic surgery or physical medicine, are now held at Roehampton in March and October The next course for orthopædic surgeons will be from March 24 to 28 inclusive, and the next for specialists in physical medicine on March 5 and 6 Those interested should apply to the Principal Medical Officer, Artificial Limbs and Appliances Centre, Roehampton House, London, S W 15

Steroid Reference Collection

Part of the Medical Research Council's Steroid Reference Collection, formerly kept at the National Institute of Medical Research, has been moved to the Postgraduate Medical School of London

All requests for compounds in the collection should now be addressed to Dr W Klyne at the School, Ducane Road, W 12 As a result of generous gifts from two industrial firms larger supplies of œstriol and 16-epi-œstriol (Organon Laboratories) and very limited supplies of racemic aldosterone (Ciba AG, Basle) are now available, these materials are intended for chemical reference purposes, and not for clinical work.

Adelaide Hospital, Dublin

An association of old students of this hospital is bei formed All old students are asked to write giving their name and addresses to the secretary, Association of Old Adelaid Students, Adelaide Hospital, Peter Street, Dublin

Major-General F C Hilton-Sergeant has succeeded Air Commodore H A Hewat as medical adviser to the British Red Cross Society

Prof W C W Nixon is to visit the United States in February to attend the annual session of the Obstetrical and Gynecological Assembly of Southern California at Los Angeles

Corrigenda The new medical dictionary which the late Dr L E Napier was preparing is to be published by the Caxton Publishing Company, Ltd, and not the Caxton Press as stated in our obituary (Dec 28, p 1343)

The Ankle-jerk in Early Hemiplegia—In Dr Buller's paper (Dec 21, p 1262) the tracings in the lower part of fig 4 were wrongly labelled The right-hand tracing recorded the left ankle jerk and the left-hand tracing the right jerk

Diary of the Week

JAN 12 TO 18

Tuesday, 14th

Royal College of Physicians of London, Pall Mall East, S W 1

5 P M Dr Aubrey Leatham Auscultation of the Heart (First Goulstonian lecture)

Royal College of Surgeons of England, Lincoln's Inn Fields, W C 2

3 45 P M Dr D J Trevan Some Mechanisms of Tumour Metastasis (Imperial Cancer Research Fund lecture)

Royal Society of Medicine, 1, Wimpole Street, W 1

8 P M *Psychiatry* Dr Doris Odlum, Dr Phyllis Epps, Dr I R C Batchelor, Dr I M H MacAdam Legal Aspects of Suicidal Acts

British Postgraduate Medical Federation

5.30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr L E Glynn Structure and Stability of Collagen in Relation to Disease of Connective Tissue

St *Mary's Hospital Medical School*, W 2

5 P M Mr Stanley Clayton Pelvic Tuberculosis

Institute of Laryngology and Otology, 330, Gray's Inn Road, W C 1

5 30 P M Prof F C Ormerod Development of the Sinuses

Birmingham Medical Institute, Harborne Road, Edgbaston

8 P M *Psychiatry* Dr Willy Mayer-Gross Psychiatry in an Industrial Community (Valedictory address)

Manchester Medical Society

8 P M *Surgery* (Clinical Sciences Building, York Place, Manchester, 13) *Mr Alan Nicholson Choledochoscopy*

Wednesday, 15th

Royal Society of Medicine

8 15 P M *General Practice* Dr R E Hope Simpson, Dr A T Roden, Dr J M Ritchie The Common Cold

Institute of Dermatology, Lisle Street, W C 2

5 30 P M Dr Arthur Tickner *Biochemistry of Hormones, II*—Non Steroids

Institute of Diseases of the Chest, Brompton, S W 3

5 P M Dr N S Plummer Broncho-Pulmonary Aspergillosis

Royal Faculty of Physicians and Surgeons of Glasgow, 242, St Vincent Street, Glasgow

5 P M Dr Sheila Sherlock Hepatic Coma (Lock lecture)

Thursday, 16th

Royal *College of Physicians of London*

5 P M Dr Leatham Auscultation of the Heart (Second of two Goulstonian lectures)

British Postgraduate *Medical* Federation

5 30 P M (London School of Hygiene and Tropical Medicine) Prof G Payling Wright Cell Regeneration and Pathological Processes

British Institute of Radiology, 32, Welbeck Street, W 1

8 P M *Dr J R Mallard, Dr A W G Goolden* Use of ^{131}I in Serial Tests, Double Isotope Investigations, and Normal Variations of Thyroid Function Dr K E Halnan Advantages Obtainable from use of ^{132}I for Thyroid Function Tests

Royal Society of Tropical *Medicine* and Hygiene, 26, Portland Place, W 1

7 30 P M Dr A R D Adams, Prof A W Woodruff, Mr D P Choyce, *Dr Frank Hawking, Dr W E Kershaw* Onchocerciasis

Liverpool Medical Institution, 114, Mount Pleasant Liverpool, 3

8 P M Dr A C Kirby Dr Philip Pinkerton, Mr P P Rickham, Dr Thomas Seager Enuresis

Manchester Medical Society

8 P M *Anæsthetics* (Staff House, University of Manchester) *Dr* W J Glover Aspects of Pædiatric Anæsthesia Dr Elizabeth Hurley Aspects of *Thiopentone*

University of St Andrews

5 P M (Queen's College, Dundee) *Mr* D J Waterston Emergency Surgery in the New Born

Friday, 17th

Royal Society of *Medicine*

5 P M *Epidemiology and Preventive Medicine* Mr R G Veryard Mr A T Lawrence, Dr P J Lawther, Dr Bernard Wa Weather and Disease

8 15 P M *Radiology* Miss Geraldine Barry, Mr G W Bl, Dr A W G Goolden Thyroid Carcinoma

Postgraduate *Medical* School, Ducane *Road*, W 12

10 A M Mr W B Gabriel Prolapse of the Rectum

4 P M *Dr D V Hubble* Chronic Thyroiditis

The Lancet · Saturday 18 January 1958

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

FACT AND THEORY *

F J Browne

M D Aberd, D Sc Edin, F.R.C S E, F R C O G

EMERITUS PROFESSOR OF OBSTETRICS AND GYNÆCOLOGY IN THE NIVERSITY OF LONDON, CONSULTING OBSTETRIC SURGEON, UNIVERSITY COLLEGE HOSPITAL, LONDON

A DISCUSSION at the Royal Society of Medicine, London, n the Ætiology of Pre-eclampsia (*Proceedings of the Royal Society of Medicine* 1957), though of great interest nd presenting new data bearing on pathogenesis, seemed o fail in its presentation of all the facts as well as in its ack of any precise conclusions regarding the ætiology of pre-eclamptic toxæmia and eclampsia

It has long seemed to me that, thanks to the researches n Great Britain, the United States, and elsewhere, specially in the past ten years, we now have all the essenial facts bearing on the ætiology of eclampsia, and that hey resemble the pieces of a jig-saw puzzle and only need o be assembled in proper sequence to provide an acceptble explanation of eclampsia, including its onset two r three days after delivery

Any satisfactory explanation of the ætiology of eclampsia must explain (1) why it occurs only in association with pregnancy and only in man, (2) its preference for first pregnancies (75% of cases), (3) why it sometimes occurs n pregnancy with hydatidiform mole and no fœtus, and that very early in pregnancy (say from the 12th to the 16th weeks), (4) why it is five or six times as common in win as in single pregnancy, (5) why it occurs in 50% of chronic hypertensive pregnancies, (6) its greater frequency n diabetic pregnancy, (7) why it is often associated with "red infarcts" in the placenta, or with concealed accidental hæmorrhage, and sometimes with renal cortical necrosis, and (8) why it often occurs two or three days after delivery (10% of all cases) This last has been the chief obstacle to the acceptance of all published theories, ncluding those of Young (1914), Paramore (1929), Beker (1948), Van Bouwdijk Bastiaanse and Mastboom (1950), Parviainen et al (1950a and b), Louros and Kairis (1951), Sophian (1953), Theobald (1955), and Bartholomew et al (1957)

Hormones in Normal Pregnancy

In normal pregnancy the anterior lobe of the pituitary gland hypertrophies and produces excess of corticotrophin This is no doubt due to œstrogens secreted by the placenta, which, besides the fœtus, is the only new organ in the pregnant woman

Corticotrophin is also produced by the placenta (Cohen and Kleinberg 1952, Assali, Hamermesz, and Ross 1954) Under this double stimulus the adrenal cortex undergoes hyperplasia and secretes excessive amounts of cortical metabolites, including glucocorticoids (11-oxycorticosteroids), which have an anti-insulin effect on carbohydrate metabolism and are the basis of the well-known delayed sugar-tolerance curve characteristic of normal pregnancy Under the influence of corticotrophin the adrenal cortex also secretes excess of the mineralocorticoids (11-deoxycorticosteroids), which retain sodium, chloride, and water Aldosterone, though probably largely responsible for the œdema both of normal pregnancy and of toxæmia, does not seem to be under the influence of the anterior lobe of the pituitary gland or of corticotrophin but to be regulated by sodium and water balance

At this point let me cite some rather striking evidence of the powerful sodium-retaining and pressor effects of adrenocortical compounds

Ferrebee et al (1939) treated 13 cases of Addison's disease with deoxycortone acetate or propionate This caused a striking retention of salt and water, the urine diminishing to 410 ml in twenty-four hours in one patient receiving a daily dose of 15 mg The blood-pressure rose from subnormal to normal levels in two to four weeks, and in 3 of the cases it rose gradually to 160/92, 160/110 and 146/108 mm Hg Of the 13 patients 10 developed œdema, varying from mild puffiness of the face and ankles to massive anasarca

Altschule and Zamcheck (1942) reported the case of a man, aged 43, who had asthma for many years but no evidence of adrenal cortical insufficiency Because of eczema, which he had had for years, sodium chloride 5 g by mouth daily and extract of suprarenal cortex 1 ml daily intramuscularly had been prescribed At that time his blood-pressure was 120/80 mm Hg and serum-protein level 5 9 g per 100 ml He received altogether 7 ml of extract of suprarenal cortex in the daily doses Severe œdema developed in his legs and soon involved his whole body, and in consequence he was admitted to hospital He then had rapid respiration, dyspnœa, orthopnœa, œdema of face, arms, legs, and trunk, and effusion into his body cavities His urine contained much albumin, casts, and a few red blood-cells His blood-pressure was 200/110 mm Hg and serum-protein level 4 42 g per 100 ml There was no evidence of congestive heart-failure Altschule and Zamcheck considered that "the syndrome closely resembles that produced by a diffusely active vascular toxin" The lowered serum-protein level suggests injury to the capillary walls by the "vascular toxin"

In this connection it is of interest to recall that examination of the œdema fluid in 3 cases of gross œdema in severe pre-eclamptic toxæmia in the obstetric department of University College Hospital, London, showed protein levels of 0 5, 0 57, and 0 9 g per 100 ml Since the normal protein level in interstitial fluid is exceedingly low (less than 0 1 g per 100 ml), this increase clearly indicates injury to the capillaries, an additional cause of the often rapidly forming œdema of pre-eclamptic toxæmia Incidentally this demonstration of injury to the capillaries by a vascular toxin justifies the retention of the term "toxæmia of pregnancy"

Though the deoxycortone acetate used by Ferrebee et al (1939) was a synthetic compound and is probably not produced to any great extent by the adrenal glands, its action in causing œdema and hypertension is of great interest It is probable that the chief cause of œdema in pre-eclamptic toxæmia is an increased secretion of salt- and water-retaining hormone by the adrenal cortex, but a contributory factor may be antidiuretic hormone, which Hawker (1952, 1957) has shown to be increased in the plasma of patients with pre-eclamptic toxæmia compared with normal pregnancy Hawker has found too that, in normal pregnancy, this hormone is kept in check by a placental enzyme which does not do so in pre-eclamptic toxæmia

We shall presently see that hydrocortisone (compound F) can cause in laboratory animals as great a rise of blood-pressure as can deoxycortone acetate In passing it is important to note that deoxycortone acetate does not raise the blood-pressure in healthy pregnant women In 1946, during my own investigations of the cause of the hypersensitivity of the vascular system in toxæmia, I was surprised to find that injected extract of suprarenal cortex in the same doses as used by Altschule and Zamcheck (1942) had no effect whatever in raising the blood-pressure in healthy pregnant women The probable reason for this has now come to light

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Hypertensive effects of Corticotrophin, Cortisone, and Hydrocortisone

Hydrocortisone and cortisone raise the blood-pressure, both systolic and diastolic, in rats at least as much as and probably more than does deoxycortone acetate after two weeks' treatment in intact (non-adrenalectomised) rats (Friedman et al 1952, Knowlton et al 1952) It is now well known that hypertension occasionally develops during therapy with corticotrophin and with cortisone (Zweifach and Shorr 1950, Cope and Hurlock 1954) Perera (1950) observed the effect of corticotrophin on the resting blood-pressure of 13 non-pregnant patients, a rise occurred in the great majority In one patient with hypertension the administration of corticotrophin 100 mg daily for nine days was followed by a rise of blood-pressure, hypertensive encephalopathy, and mental confusion

Increase of Corticosteroids in Normal and in Toxæmic Pregnancy

Bayliss et al (1955) followed the plasma levels of 17-hydroxycorticosteroids at monthly intervals through the normal pregnancies of 30 women The level rose progressively during normal pregnancy, becoming in some cases very high, after delivery the level fell and was normal again after a week Gemzell (1953) found that the concentration of 17-hydroxycorticosteroids (which include hydrocortisone) in the blood in the last three months of normal pregnancy was four times the pre-pregnancy value Immediately after delivery it increased to seven times the normal value, but by the sixth day it had fallen to pre-pregnancy level The significance of this rise immediately after delivery will be discussed later

Many investigators have found that, in toxæmia, the urinary excretion of corticosteroids is considerably larger than in normal pregnancy (Tobian 1949, Parviainen 1950a and b, Chart et al 1951, Lloyd et al 1952, Venning et al 1954)

I am aware that Assali et al (1955) found that the blood levels of 17-hydroxycorticosterones were not raised in toxæmia compared with normal pregnancy The glucocorticoids alone, however, were estimated, not the mineralocorticoids, which are probably the hormones chiefly involved in pregnancy toxæmia Assali et al (1955), commenting on their results, state

> " By excluding glucocorticoids from involvement in toxæmia our results lend support to the work of the aforementioned investigators (i e , Venning, Tobian, Lloyd et al) which indicates that mineralocorticoids may be the hormones involved in this abnormality "

It should be here noted that Chart et al (1951) found much increased excretion of a sodium-retaining factor in toxæmic pregnancy but no parallel increase in the excretion of 11-oxysteroids (glucocorticoids)

Cushing's Syndrome and Normal Pregnancy

There are several resemblances between normal pregnancy and Cushing's disease, which is now regarded as due, in most cases, to hyperplasia of the adrenal corte J S L Browne, indeed, has spoken of normal pregnan as "a kind of physiological Cushing's syndrome Examples of this resemblance are insensitivity to insul adiposity, osteoporosis, striæ, sodium retention, a hypertension, which is present in Cushing's syndro in 90% of cases Study of 15 cases of normal pregnan by Bush and Pickering (Bush 1953) has shown that t blood-level of 17-hydroxycorticosterone is within t range of that found in Cushing's disease

> " Thus the increased rate of adrenocortical secretion pregnancy, indicated by clinical findings and estimations urinary steroids, is also associated with an increased conce tration of adrenocortical hormone in the peripheral veno blood " (Bush 1953)

I have discussed Cushing's syndrome at some leng because it shows that blood-pressure-raising hormon are produced by the adrenal cortex in normal pregnanc I shall suggest later that hypertension similar to that Cushing's disease would develop in every pregnant wom if it were not for the protective placenta Striæ oft appear in pregnancy on the upper and outer aspects the thighs, where they could not be due to stretching the skin or to deposit of fat over the fascia lata They a very well-known side-effects of cortisone, and thoug they are usually present in Cushing's disease, even thin legs, they may be absent, as they often are, pregnant women

The Protective Placenta

It will be evident that the normal overaction of th anterior lobe of the pituitary gland and of the adren cortex can cause the syndrome of pre-eclamptic toxæmi including œdema, hypertension, and albuminuria Wh then does not every pregnant woman become hype tensive? That she becomes œdematous is well know and that half the weight gain of normal pregnancy due to retention of water—i e , 12 lb or 6 litres of water

In 1948 it was shown that there is present in the norm human placenta and decidua a highly active mono-amin oxidase that can inactivate vasoconstrictor amines—e g adrenaline and tyramine Its activity increases as the placen matures, and is diminished or inhibited by a decrease in t oxygen tension of the medium in which it acts (Luschinsky a Singher 1948, Thompson and Tickner 1949) The significan of this work could not be appreciated in 1948, because work had been done on the maternal placental blood-flo Browne and Veale (1953), however, by injecting radioacti sodium into the placental blood sinuses and measuring its ra of disappearance in healthy, pre-eclamptic, and chronical hypertensive women, showed that there was a reduction about half in the pre-eclamptic and chronically hypertensi women compared with the healthy women This reductio could decrease the oxygen tension within the placenta, and th finding of a decreased oxygen tension in the cord blood toxæmia (Walker 1954) suggests that this actually happens

It will be clear, therefore, that in normal pregnanc when the placenta has not been made ischæmic, press substances can be wholly or partly destroyed, in placent ischæmia, however caused, the enzyme cannot exert i anti-pressor activity, with consequent failure of degrad tion of vasoconstrictor substances produced by th adrenal glands

Corroborative evidence of this activity is found in th fact that, though corticotrophin causes hypertension non-pregnant women, it does not do so in health pregnant women Assali and Suyemoto (1954) ga intramuscular corticotrophin 120 mg for four, five, an

Sensitisation of Vascular System

That the vascular system is hypersensitive in pre-eclamptic toxæmia was first demonstrated by Schockhaert and Lambillon (1937) and Dieckmann and Michel (1937), and confirmed by De Valera and Kellar (1938) and myself (Browne 1943)

That this hypersensitivity is not hereditary or constitutional but acquired between about the seventeenth week and the time at which toxæmia becomes clinically manifest was shown by me in 1946 (Browne 1946), when I found evidence that its cause was chorionic gonadotrophin. This finding that the sensitisation is acquired in the course of pregnancy rules out the suggestion that pre-eclamptic toxæmia develops only in women with a familial predisposition to chronic hypertension I was unable to pick out, by the cold pressor test, women who would develop toxæmia in later pregnancy (Browne 1940)

Byrom (1937) produced, in rats, lesions closely resembling those of eclampsia—focal necrosis of the liver and symmetrical cortical necrosis in the kidneys—by injecting vasopressin. He believed the lesion to be due to arteriolar spasm. He also found that the sensitivity to vasopressin could be increased ten times by œstrogenic hormones, and that, in unspayed rats, the sensitisation could equally well be brought about by gonadotrophic hormones

All the evidence therefore goes to show that sensitisation of the vascular system, acquired from whatever cause in pregnancy, plays a part in the ætiology of toxæmia

I am aware that the adrenocorticosteroids are not mono-amines They are all combinations of carbon, hydrogen, and oxygen, and I suggest that the normal placenta contains an oxygen-sensitive oxidase that can inactivate them This is a matter for further investigation

What is the purpose of this elaborate mechanism that has been developed during the course of normal pregnancy in the internal secretory organs, including the placenta? I suggest that it is designed to protect the fœtus from the dangerous consequences of low blood-pressure that would otherwise occur, and increase as pregnancy advances, through pooling of blood in the maternal placental blood lake combined with the erect posture (Theobald 1955) The result is that, in the great majority of cases, the blood-pressure is nicely adjusted to that end and kept at normal levels, neither hypotensive nor hypertensive, by the protective placenta Through various causes this healthy adjustment sometimes fails, and pre-eclamptic toxæmia and eclampsia are the consequences There is no need to think of them as "diseases of adaptation", because the stimulus for the adrenal cortex is in the placenta

Summary

Under the influence of corticotrophin produced by the placenta and the anterior lobe of the pituitary gland (the latter stimulated by œstrogens secreted by the placenta) the adrenal cortex in pregnancy produces excess of cortical metabolites, including glucocorticoids and mineralocorticoids

There are several resemblances between normal pregnancy and Cushing's syndrome, which is usually due to hyperplasia of the adrenal cortex and is in 90% of cases accompanied by hypertension In normal pregnancy there must therefore be a pressor substance produced in excess (compared with the non-pregnant individual) by the adrenal cortex The blood in normal pregnancy contains 17-hydroxycorticosteroids equal in amount to or exceeding those in Cushing's syndrome.

Every pregnant woman would become hypertensive if it were not for the protective placenta which furnishes, it is suggested, an oxygen-sensitive oxidase that inactivates pressor hormones from the adrenal cortex The presence of this enzyme would explain the fact that cortical hormones, which in the non-pregnant individual cause hypertension and œdema, are without effect in healthy pregnant women If from any cause the placenta is made ischæmic and its oxygen tension lowered, the protective enzyme is made ineffective, and hypertension results

The excess of chorionic gonadotrophin present in pre-eclamptic toxæmia can be explained by its non-destruction There is evidence that it causes the hypersensitivity of the vascular system known to exist in pre-eclamptic toxæmia.

In 25–30% of women who have been normotensive during pregnancy and labour the blood-pressure reaches hypertensive levels in the first three days after delivery This can be correlated with Gemzell's (1953) findings that the level of 17-hydroxycorticosteroids in the blood before labour is increased by nearly 100% immediately after the birth of the placenta Dangerous eclamptogenic rises of blood-pressure often occur in toxæmic patients after delivery It is suggested that the birth of the placenta and the loss of its inactivating effect on pressor hormones explain the onset of eclampsia in the first three days of the puerperium in women who have had pre-eclamptic toxæmia before delivery

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eclampsia within the first three days of the puerperium Fits occurring after that time are, I suggest, due to one of two causes primary cerebral venous thrombosis (Martin and Sheehan 1941) and subarachnoid hæmorrhage In all such cases a neurologist should be called in and, when subarachnoid hæmorrhage is a possibility, lumbar puncture should be done to exclude blood in the cerebrospinal fluid

If this explanation of the absence of hypertension in normal pregnancy and of the occurrence of eclampsia in the first three days after delivery is correct, we would expect a rise of blood-pressure after the birth of the placenta in women whose blood-pressure has been normal throughout pregnancy and labour I have not been able to find any reference to this in textbooks, and it seems to have been assumed that the blood-pressure is always normal Examination of blood-pressures of such women at the Royal Hospital for Women, Sydney, and at the Postgraduate Medical School of London, has, however, shown that 20–30% are hypertensive in the first three days after delivery This is remarkable when it is considered that these women are at rest, are tired after labour, and have often lost a considerable amount of blood Intramuscular ergometrine 0 5 mg was given routinely at the end of the second stage, but the puerperal blood-pressures were not taken until between twelve and twenty hours after delivery, and some much later It is therefore unlikely that any of the hypertensions were due to ergometrine

Rise of Blood-pressure in Toxæmic Patients after Delivery

During the last week several examples of this have come to my notice without seeking or searching

(1) *Mrs A,* aged 27, first pregnancy, multiple pregnancy, and pre-eclamptic toxæmia *May 1, 1957* membranes stripped and medical induction given *May 3* artificial rupture of membranes and oxytocin drip *May 4* episiotomy and breech extraction of first infant, forceps delivery of second, manual removal of placenta because of postpartum hæmorrhage, intramuscular ergometrine 0 5 mg given, after delivery blood-pressure rose remarkably to 170/120 mm Hg From this time onward the patient progressively deteriorated and died at 1 45 A M on *May 5* Necropsy revealed a liver with findings typical of eclampsia

(2) Bulfin and Lawler (1957) review 234 sets of twins delivered beyond seven months' gestation, and state that there were 12 cases "in which the excessive rise in blood pressure post-partum resulted in headache, nausea and visual disturbances, creating all the appearances of impending eclampsia In retrospect we now feel that the injudicious use of ergonovine in these patients already toxæmic could have been responsible for the fulminating post-partum symptoms" They state that intravenous ergometrine maleate occasionally causes acute hypertension which persists from half an hour to four hours "The hypertensive effect of this drug seems to be even more pronounced in the patient whose uterus is contracting following distension from a twin pregnancy"

(3) Dugan and Black (1957), discussing kyphoscoliosis in pregnancy, review 39 pregnancies in twenty-two hospitals and give a detailed account of 1 fatal case This woman had toxæmia and was delivered vaginally by forceps after pudendal block The placenta and membranes were complete, and there was no postpartum bleeding At 2 30 P M, forty-five minutes after delivery, the patient's pulse-rate was 122 and blood-pressure 148/80 mm Hg At 3 30 P M, one and three-quarter hours after delivery, her blood-pressure was 180/100 mm Hg She had a generalised convulsion, which lasted about three minutes Her condition steadily deteriorated, and she died at 7 P M During labour she had been given pethidine and scopolamine and, because of severe restlessness during delivery, intravenous morphine sulphate gr $^1/_6$ There is no note about whether ergot was given or not

Eclamptic Fits

These are caused by a rapidly rising systolic bloo pressure causing hypertensive encephalopathy, and cerebral œdema

That a rapidly rising systolic blood-pressure alone can cau convulsions is shown by Byrom's (1954) experiments on ra He removed one kidney and clamped the renal artery of t other In the weeks after the operation the systolic bloo pressure rose and ultimately, when it reached an excessiv high level (over 200 mm Hg), especially if it rose steeply, fa convulsions came on Through a 'Perspex' window in th rat's skull spasm was seen in the cerebral arterioles during th convulsions

Œdema of the brain alone can cause fits Rowntree (192 showed that by giving 50 ml of water per kg of body-weig to dogs every half-hour—i e, faster than the kidneys cou excrete it—he could produce convulsions, coma, and dea in a few hours Necropsy revealed œdema of the connectiv tissues, liver, kidneys, and brain Rowntree demonstrat increased intracranial pressure during life and believed this t be the cause of the convulsions

It is possible that hypertension and œdema can suppleme each other as eclamptogenic agents, that fits can occur if systol blood-pressure rises quickly to a high level with little or n œdema, as in Byrom's (1954) rats, and that they may occur i there is cerebral œdema alone if the blood-pressure is normal o near normal, as in Rowntree's (1923) dogs

Cerebral dysrhythmia may possibly predispose to fits, but the evidence is inconclusive (Rosenbaum and Maltby 1943, Parviainen et al 1950a and b, Macintosh 1952, James 1955, Poidevin 1955) Recently I saw a patient who had pre-eclamptic toxæmia and idiopathic epilepsy, but eclampsia did not develop

This view of the cause of eclamptic fits received support from the results in Cincinnati, U S A, where treatment of eclampsia is based on the assumption that the fits are due to cerebral vascular spasm, and that if it is relieved they will cease This is achieved by giving alkaloids of veratrum viride, œdema is also treated with intravenous dextrose, and magnesium sulphate, 50% solution, is injected intramuscularly as a sedative and anticonvulsant to relax the cerebral vasospasm (McCall and Sass 1956) No other sedatives are given To date 205 consecutive cases have been reported with only 3 deaths, 2 of which took place in pre-antibiotic days from puerperal sepsis, one fourteen days and the other sixty-five days after cure of the eclampsia and delivery This is an uncorrected maternal mortality of 1 5% (Bryant and Fleming 1940, Garber 1953)

Role of Diet in Causing Toxæmia

The greatly increased frequency of eclampsia in patients with beriberi (King and Ride 1945) and in areas of the United States where pellagra is endemic suggests that vitamin-B complex may be essential for the action of the placental enzymes Hipsley (1953) has found that eclampsia is much less common among races that consume large amounts of fibre in their diet I think that the fibre may contain vitamin B Possibly other dietary factors—e g, calcium and vitamin D—are also important in this connection (Theobald 1955) Perhaps a high-carbohydrate diet, by raising the blood-sugar level, calls for a greater output of insulin and therefore of growth hormone to provide it, and as a consequence of this an increased output of corticotrophin This might explain the value of a low-carbohydrate diet in preventing toxæmia (Stevenson 1952, Hamlin 1952, J Woodhill, personal communication, and others)

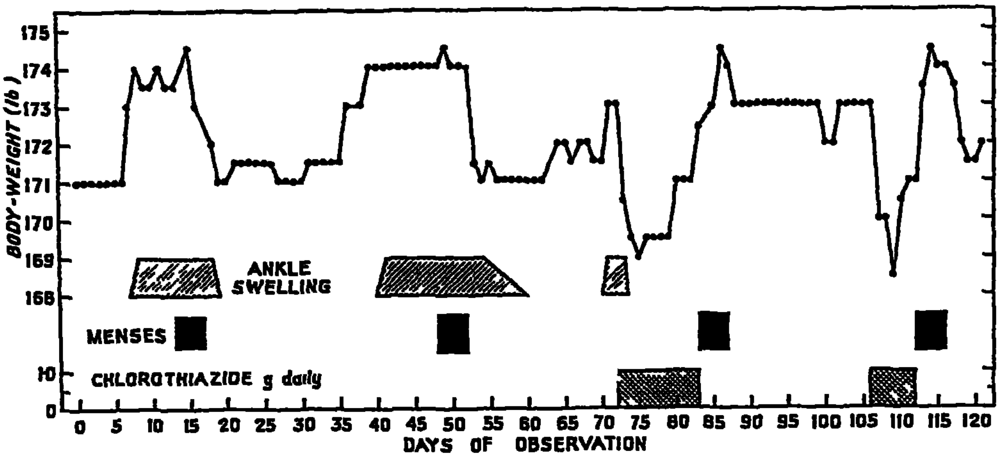

Fig 4—Patient no 18 with premenstrual œdema.

Chlorothiazide given before the third and fourth menstrual periods largely controls the symptoms and weight gain, but should have been continued during the menstruation

sodium, chloride, or bicarbonate levels were observed, but the serum-potassium level tended to fall (as shown in fig 2), and in all eleven patients whose urinary excretion of electrolytes was studied there was increased loss of potassium In three patients the serum-potassium level dropped to below 3 mEq per litre without symptoms of potassium depletion, and a fourth had such symptoms with a serum-potassium level of 3 1 mEq Chlorothiazide was given daily to three of these patients, and for 4 days each week to the fourth In two the daily intake of sodium was 22 mEq, in one it was 87 mEq, and in the fourth, with nephrosis and heavy proteinuria, it was 218 mEq

No changes in liver-function tests, white-cell and platelet counts, or hæmoglobin levels were seen None of the patients developed gastro-intestinal or other symptoms attributable to chlorothiazide, with the single possible exception of the cirrhotic patient (no 21), who became anorexic and felt unwell

Comparison with Mersalyl

A detailed comparison of the potency of chlorothiazide and mersalyl will be reported elsewhere It will be seen, however, from table I and from fig 2 that patients who responded poorly or not at all to bi-weekly injections of mersalyl may have a satisfactory diuresis on chlorothiazide

Refractoriness to mersalyl, despite persisting œdema, may be due to the severity of the patient's condition, a low glomerular filtration-rate, or electrolyte imbalance (Stock et al 1951) None of these eleven patients who responded poorly to mersalyl had hypochloræmic alkalosis, hyponatræmia, or hypokalæmia, yet five of them gave a good and four a fair response to chlorothiazide Fig 3, for example, shows little fall in weight on days 20 and 22, when mersalyl alone was given, but a good diuresis and weight loss when continuous chlorothiazide treatment was started on day 24

Chlorothiazide and mersalyl given together produce a greater diuresis than either given alone For example, in fig 3 electrolyte and water excretion was greater on day 12, when the two agents were given together, than on days 6, 10, and 14, when chlorothiazide was given alone, or on days 16, 20, and 22, when mersalyl was given alone Furthermore, chlorothiazide may increase the response to mersalyl in patients who have become mersalyl-resistant, if the two agents are given together (Bayliss et al 1958) This enhanced response to combined treatment may be of clinical value in patients whose œdema fails to clear completely on chlorothiazide alone, and suggests that chlorothiazide and mersalyl may influence two different mechanisms for the tubular reabsorption of chloride

Discussion

The ideal diuretic should (*a*) be effective by mouth, (*b*) be at least as potent as mersalyl, (*c*) cause a proportionate loss of sodium, chloride, and water, (*d*) not induce any electrolyte imbalance, (*e*) not lose its effectiveness (so that it can be given continuously if necessary and allow the seriously incapacitated patient to eat a diet containing a palatable amount of sodium chloride), and (*f*) be devoid of toxic effects Such a substance does not exist, but chlorothiazide meets many of these desiderata It is effective by mouth, causes almost equimolar loss of sodium and chloride, and in our experience has been outstandingly free from toxic effects It may cause potassium depletion, and is not always therapeutically effective, but it would be difficult to imagine any substance that would unfailingly induce a diuresis in severe congestive cardiac failure, particularly when the glomerular filtration-rate is much reduced Many of the cardiac patients who showed a poor or fair response to chlorothiazide were old, chronically ill, and resistant to other forms of treatment Indeed it is more remarkable that several of this type (e g, nos 1, 5, 7, 8, and 16) responded to chlorothiazide at all

Potassium depletion and hypokalæmia may develop during treatment with any diuretic that increases the excretion of chloride or bicarbonate, and the more potent the diuretic the more likely is this to happen Usually the increased amount of chloride excreted will be accompanied by sodium, but, if the amount of available sodium is reduced—either because of rigid dietary restriction, or because of intense tubular reabsorption of sodium—potassium may be excreted instead Our experience shows that continuous daily administration of 2 g chlorothiazide may cause potassium depletion, and as daily treatment may be necessary for a long time in severely ill refractory patients, a careful watch should be kept on the serum-potassium level, and daily supplements of potassium chloride 2–6 g in capsules should be given to prevent hypokalæmia In less severe cases which respond quickly, continuous administration of chlorothiazide 2 g daily is necessary for only a few days, and thereafter a smaller dose, 1 0–1 5 g daily, can be used and maintenance therapy given intermittently on 3–4 days each week

Summary

The value of chlorothiazide, a non-mercurial orally effective diuretic, has been assessed in 24 œdematous

TABLE II—SUMMARY OF RESULTS

Disease	Response*		
	Good	Fair	Poor
Congestive heart-failure			
Ischæmic heart-disease	4	1	1
Hypertensive heart-disease	5	3	0
Valvular heart-disease	1	1	1
Hepatic cirrhosis	0	0	1
Nephrosis	0	1	0
Premenstrual œdema	3	0	0
Miscellaneous	1	1	0
Total	14	7	3

*See text.

with a weight loss of 15 lb in 9 days The serum-potassium level fell, and, when the sodium intake was increased from 87 to 218 mEq per day, the œdema recurred with a weight gain of 4 lb

Another hypertensive patient (no 13), with renal insufficiency, lost 12 lb spontaneously during the first 10 days in hospital When he was almost œdema-free, chlorothiazide increased the natriuresis and induced a further loss of 6 lb in the next 10 days, but the blood-urea rose from 50 mg per 100 ml on admission to 150 mg No abnormality of the electrolytes was found, and as there was no dehydration (judged by the extracellular-fluid volume, which had fallen from 23 0 litres to a normal value of 15 4 litres), the azotæmia was attributed to a further deterioration in renal function

The third patient (no 14), who showed only a fair response, became œdema-free on chlorothiazide, but increased activity led to some reaccumulation of fluid

Valvular heart-disease—There were three patients in this group

One (no 15) responded well, losing 10 lb in weight and becoming œdema-free

A second (no 16), who had been in chronic congestive failure for 3 years with frequent hospital admissions, was readmitted with gross œdema Bi-weekly injections of mersalyl for 17 days produced no improvement, and he gained 3 lb Chlorothiazide (2 g daily for a week and then 3 g daily for 10 days) caused only a 5 lb loss of weight The addition of mersalyl induced a further diuresis, and the weight fell another 10 lb This result, which can only in part be attributed to chlorothiazide (although seemingly as a result of its use the patient became responsive to mersalyl), has been classified as fair The third patient (no 17) had been in failure for many months with mitral stenosis, aortic incompetence, tricuspid incompetence, and cardiac cirrhosis No significant improvement followed treatment with chlorothiazide or mersalyl (with or without ammonium chloride) either singly or in combination

Premenstrual œdema

All three patients responded well to chlorothiazide given 7–10 days before the onset of their menses, when symptoms were liable to start The result in 1 of these patients is shown in fig 4

Cirrhosis

One patient with alcoholic cirrhosis, ascites, and œdema of the legs lost 7 lb in 8 days Treatment was stopped because she felt increasingly anorexic and unwell, but as no electrolyte abnormality was found, her symptoms were probaby more related to sudden withdrawal of alcohol than to chlorothiazide

Nephrosis

This patient with chronic spinal tuberculosis had amyloid nephrosis, shown by finger-clubbing, hypoalbuminæmia, heavy proteinuria, and 75% retention of congo-red

Chlorothiazide induced a striking diuresis and weight loss of 26 lb, the extracellular-fluid volume falling from 29 9 to 18 5 litres Despite continuing hypoproteinæmia the patient was œdema-free, and the dose of chlorothiazide was reduced from 2 to 1 g daily Although he was on a high-protein diet containing 218 mEq of sodium, hypokalæmia of 2 8 mEq per litre developed, and a potassium supplement of 80 mEq daily was given to correct this The œdema returned and was not controlled until the dose of chlorothiazide was raised to 4 g daily Chlorothiazide did not increase the urinary concentration of protein, 40 g daily being excreted during the diuretic phase

Miscellaneous

One patient (no 23) with œdema of the legs and abdominal wall due to malignant obstruction of the inferior vena cava showed a good response and lost 13 lb in 14 days Another with cirrhosis (no 24), who developed œdema after a portacaval anastomosis, was only fairly well controlled on chlorothiazide 1 g given for 4 days each week, and became hypokalæmic

Electrolyte Disturbances and Toxic Effects

On the intake of sodium chloride given to these patients no significant changes in serum

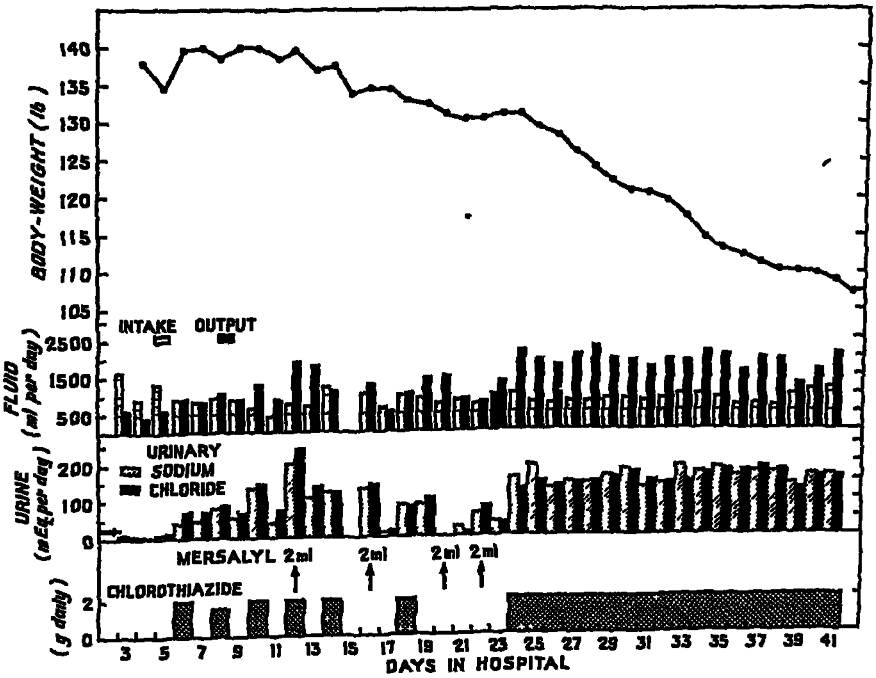

Fig 3—Patient no 7, aged 71, with hypertensive heart-disease

The dietary sodium intake (22 mEq daily) is shown by the arrow on the sodium and chloride scale Note gradual increase in sodium and chloride excretion on days 6, 8, and 10 when chlorothiazide is given on alternate days On day 12 the combination of mersalyl and chlorothiazide causes a further increase in the water and sodium diuresis On day 22 there is a poor response to mersalyl alone and no weight loss A good response follows 2 g chlorothiazide daily started on day 24

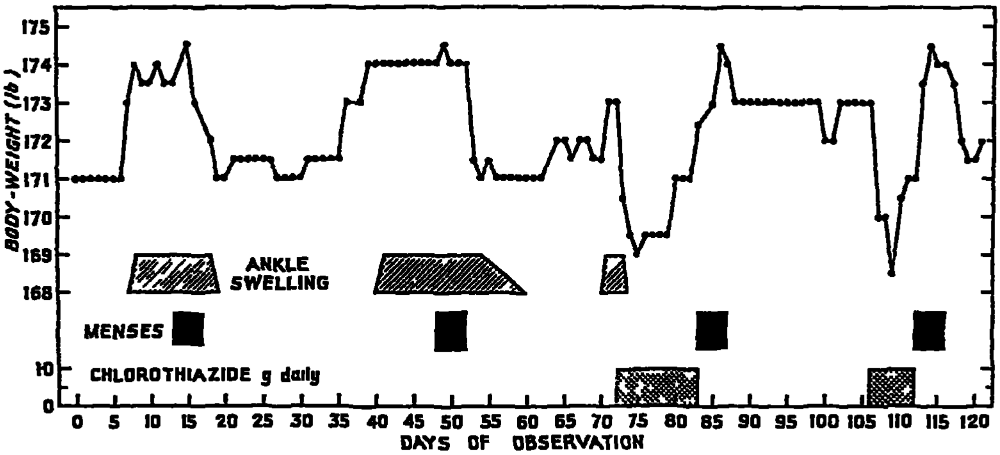

Fig 4—Patient no 18 with premenstrual œdema.

Chlorothiazide given before the third and fourth menstrual periods largely controls the symptoms and weight gain, but should have been continued during the menstruation

sodium, chloride, or bicarbonate levels were observed, but the serum-potassium level tended to fall (as shown in fig 2), and in all eleven patients whose urinary excretion of electrolytes was studied there was increased loss of potassium In three patients the serum-potassium level dropped to below 3 mEq per litre without symptoms of potassium depletion, and a fourth had such symptoms with a serum-potassium level of 3 1 mEq Chlorothiazide was given daily to three of these patients, and for 4 days each week to the fourth In two the daily intake of sodium was 22 mEq, in one it was 87 mEq, and in the fourth, with nephrosis and heavy proteinuria, it was 218 mEq

No changes in liver-function tests, white-cell and platelet counts, or hæmoglobin levels were seen None of the patients developed gastro-intestinal or other symptoms attributable to chlorothiazide, with the single possible exception of the cirrhotic patient (no 21), who became anorexic and felt unwell

Comparison with Mersalyl

A detailed comparison of the potency of chlorothiazide and mersalyl will be reported elsewhere It will be seen, however, from table I and from fig 2 that patients who responded poorly or not at all to bi-weekly injections of mersalyl may have a satisfactory diuresis on chlorothiazide

Refractoriness to mersalyl, despite persisting œdema, may be due to the severity of the patient's condition, a low glomerular filtration-rate, or electrolyte imbalance (Stock et al 1951) None of these eleven patients who responded poorly to mersalyl had hypochloræmic alkalosis, hyponatræmia, or hypokalæmia, yet five of them gave a good and four a fair response to chlorothiazide Fig 3, for example, shows little fall in weight on days 20 and 22, when mersalyl alone was given, but a good diuresis and weight loss when continuous chlorothiazide treatment was started on day 24

Chlorothiazide and mersalyl given together produce a greater diuresis than either given alone For example, in fig 3 electrolyte and water excretion was greater on day 12, when the two agents were given together, than on days 6, 10, and 14, when chlorothiazide was given alone, or on days 16, 20, and 22, when mersalyl was given alone Furthermore, chlorothiazide may increase the response to mersalyl in patients who have become mersalyl-resistant, if the two agents are given together (Bayliss et al 1958) This enhanced response to combined treatment may be of clinical value in patients whose œdema fails to clear completely on chlorothiazide alone, and suggests that chlorothiazide and mersalyl may influence two different mechanisms for the tubular reabsorption of chloride

Discussion

The ideal diuretic should (*a*) be effective by mouth, (*b*) be at least as potent as mersalyl, (*c*) cause a proportionate loss of sodium, chloride, and water, (*d*) not induce any electrolyte imbalance, (*e*) not lose its effectiveness (so that it can be given continuously if necessary and allow the seriously incapacitated patient to eat a diet containing a palatable amount of sodium chloride), and (*f*) be devoid of toxic effects Such a substance does not exist, but chlorothiazide meets many of these desiderata It is effective by mouth, causes almost equimolar loss of sodium and chloride, and in our experience has been outstandingly free from toxic effects It may cause potassium depletion, and is not always therapeutically effective, but it would be difficult to imagine any substance that would unfailingly induce a diuresis in severe congestive cardiac failure, particularly when the glomerular filtration-rate is much reduced Many of the cardiac patients who showed a poor or fair response to chlorothiazide were old, chronically ill, and resistant to other forms of treatment. Indeed it is more remarkable that several of this type (e g, nos 1, 5, 7, 8, and 16) responded to chlorothiazide at all

Potassium depletion and hypokalæmia may develop during treatment with any diuretic that increases the excretion of chloride or bicarbonate, and the more potent the diuretic the more likely is this to happen Usually the increased amount of chloride excreted will be accompanied by sodium, but, if the amount of available sodium is reduced—either because of rigid dietary restriction, or because of intense tubular reabsorption of sodium—potassium may be excreted instead Our experience shows that continuous daily administration of 2 g chlorothiazide may cause potassium depletion, and as daily treatment may be necessary for a long time in severely ill refractory patients, a careful watch should be kept on the serum-potassium level, and daily supplements of potassium chloride 2–6 g in capsules should be given to prevent hypokalæmia In less severe cases which respond quickly, continuous administration of chlorothiazide 2 g daily is necessary for only a few days, and thereafter a smaller dose, 1 0–1 5 g daily, can be used and maintenance therapy given intermittently on 3–4 days each week.

Summary

The value of chlorothiazide, a non-mercurial orally effective diuretic, has been assessed in 24 œdematous

patients, of whom 17 had congestive heart-failure and 11 had responded poorly to mersalyl

A daily dose of 2 g produced good results (with clearing of the œdema) in 14 patients In 7 the results were less satisfactory, and in 3 they were poor

Chlorothiazide may be effective in patients who do not respond to mersalyl, and it enhances the response to mersalyl even in patients who have become mersalyl-resistant

Except for 1 patient who developed malaise and anorexia, no toxic effects were observed

Chlorothiazide may cause potassium depletion, particularly if continuous treatment with 2 g daily is given over a long period In refractory cases this dosage may be required and should be supplemented with 2–6 g potassium chloride (sufficient to maintain a normal serum-potassium level) In less severe cases which respond quickly a smaller dose of chlorothiazide (1 0–1 5 g daily) may suffice, and for maintenance therapy the drug may be given intermittently on three or four days each week

We are grateful to Drs C J Gavey and F Dudley Hart for allowing us to study patients under their care, to Miss Margaret Wood and Miss Jill Nuttall for technical assistance, and to Messrs Merck Sharp & Dohme for generous supplies of chlorothiazide ('Saluric')

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CLINICAL EXPERIENCE WITH CHLOROTHIAZIDE

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CHLOROTHIAZIDE is a new oral non-mercurial diuretic Chemically it is 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1, 1-dioxide, a heterocyclic compound containing a sulphonamido group Preliminary studies by Ford et al (1957) have shown that it is as effective as the mercurial diuretics In vitro it inhibits carbonic anhydrase but in vivo it causes a considerable increase in the rate of excretion of chloride and sodium without producing metabolic acidosis The effect on chloride output is unlike the action of carbonic anhydrase inhibitors (Hanley and Platts 1956) and resembles the action of organic mercurial compounds

We report here our initial clinical experience with chlorothiazide in three patients with the nephrotic syndrome, one patient with ascites due to portal hypertension, and one patient with congestive heart-failure A short-term study designed to assess its effect on renal carbonic anhydrase is also described

Case-reports

Case 1—A woman, aged 38, developed the nephrotic syndrome in September, 1956 Her serum-albumin level was 1 8 g per 100 ml, urinary output of protein 25 g daily, and serum-cholesterol level 1300 mg per 100 ml However, in addition, she had hypertension (B P 190/100 mm Hg), granular casts, white and red blood-cells in her urine, and retention of urea (blood-urea level 34–62 mg per 100 ml) She has been maintained on a low-sodium diet (initially 44 mEq and later 22 mEq daily) Prolonged treatment with cation exchange resins and later with prednisone did not produce any permanent improvement

Treatment with chlorothiazide 500 mg six-hourly, started in May, 1957, caused a rapid well-marked diuresis with increased excretion of sodium and chloride Her body-weight fell by 3 9 kg in six days She then had a transient attack of abdominal pain, diarrhœa, and vomiting Chlorothiazide was withheld, and she lost 3 0 kg Renewed administration of chlorothiazide (500 mg twelve-hourly) ten days later did not cause gastro-intestinal symptoms, and she has now taken chlorothiazide intermittently—one week every alternate week—for six months without ill effect Her weight has remained steady, and she feels well and is almost free from œdema Persistent hypokalæmia has developed and is only partially controlled by an extra 40–80 mEq of potassium daily (potassium chloride 3–6 g) No clinical effects attributable to hypokalæmia can be recognised

Case 2—A woman, aged 49, developed the nephrotic syndrome in March, 1956 Her serum-albumin level was 1 7 g per 100 ml, urinary output of protein 22 g daily, and serum-cholesterol level 780 mg per 100 ml Her blood-pressure was normal Her urine contained white blood-cells and a few red blood-cells but no casts, and her blood-urea level was normal The œdema persisted despite treatment with a low-sodium diet (30 mEq daily), prednisone, and mersalyl injections Treatment with cation-exchange resin, started in September, 1956, was poorly tolerated but controlled the œdema Resins were stopped in May, 1957, and her weight increased by 2 3 kg in two weeks on a diet containing 22 mEq of sodium daily

Treatment with chlorothiazide 500 mg six-hourly was begun in June, 1957 The patient lost 2 0 kg in the next six days, with a prompt diuresis and increased excretion of sodium and chloride Since then a maintenance dose of 500 mg eight-hourly (given at first every alternate week and later for four days in each week) has controlled her œdema and body-weight There has been a tendency to hypokalæmia, and despite an extra 55 mEq of potassium daily the plasma-potassium level has on occasions fallen to 2 8 mEq per litre

Case 3—A man, aged 37, developed the nephrotic syndrome in April, 1957 His urinary output of protein is 25 g daily, serum-albumin level 1 2 g per 100 ml, and serum-cholesterol level 890 mg per 100 ml He also has hypertension (B P 140/100 mm Hg), retention of urea (blood-urea level 103 mg per 100 ml), and numerous granular casts and white and red blood-cells in his urine There had been little response to a low-salt diet and prednisone therapy

Treatment with chlorothiazide began after a control period on a low-sodium diet (22 mEq daily) 500 mg six-hourly, begun in October, 1957, caused a prompt diuresis, increased urinary excretion of sodium and chloride, and a weight loss of 4 6 kg in eleven days The intake of sodium was subsequently increased, but, when it exceeded 44 mEq daily, œdema reappeared

Case 4—A man, aged 69, developed ascites due to portal hypertension and diffuse hepatic fibrosis in August, 1955 The ascites was controlled successfully for the first sixteen months with a low-sodium diet (22 mEq daily) and weekly mersalyl injections, but over the next five months more ascitic fluid developed despite twice-weekly mersalyl injections

Treatment with chlorothiazide 500 mg six-hourly was started in June, 1957. Initially this provoked a considerable diuresis with increased urinary excretion of sodium and chloride. Two months later chlorothiazide had become ineffective, and the patient was also found to be resistant to mersalyl injections. A combination of the two treatments produced a satisfactory diuresis, and for the past three months the ascites has been controlled by continuous chlorothiazide therapy with twice-weekly injections of mersalyl 2 ml. The plasma-potassium level is 3.0–4.1 mEq. per litre despite 6 g. of potassium chloride (80 mEq. of potassium) daily.

Case 5 was a man, aged 80 years, with congestive heart-failure.

Methods

The patients were studied in hospital initially, and cases 1, 2, and 4 were subsequently followed as out-patients. They were intelligent, cooperative people who could be relied on to keep to their diets and to collect their urine accurately. Before chlorothiazide was given, there was a control period of 4–8 days on a diet of fixed sodium and chloride content. Blood-pressure and body-weight were recorded daily. Twenty-four-hour collections of urine were made, and their accuracy checked by creatinine estimations. Electrolyte and protein levels in the plasma and in the urine were determined by standard laboratory methods, and urinary glucose by the glucose-oxidase technique of Froesch and Renold (1956). In the short-term study the urine was collected by catheter, and both urine and arterial blood were kept from contact with air. The pH was estimated within 10 minutes of collection at 37°C on the pH meter described by Wynn and Ludbrook (1957). A Stadie electrode system was used and standardised with fresh phthallate buffer at pH 4.025. Titratable acidity was estimated by titration with standard NaOH to pH 7.4.

Results

Short-term Study

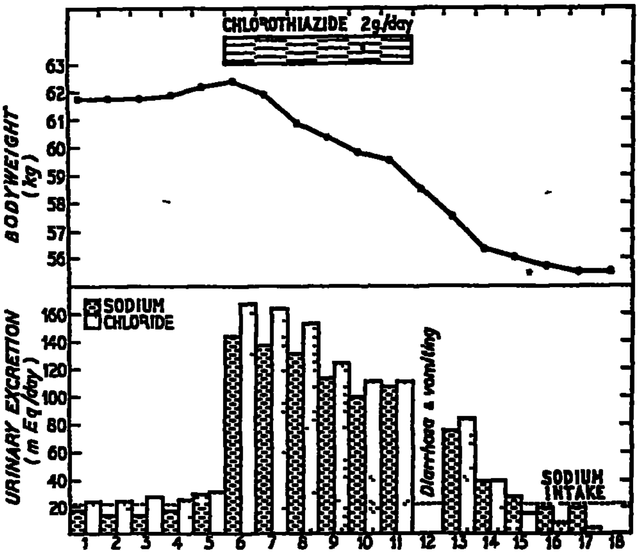

Fig. 2.—Case 1 (nephrotic syndrome): effect of initial course of chlorothiazide on body-weight and urinary excretion of sodium and chloride.

The patient selected for this had rheumatic heart-disease and benign essential hypertension. She had had congestive heart-failure, but this had responded to rest in bed, a low-sodium diet, and digitalis. She was able to concentrate the urine to sp. gr. 1.027, and her blood-urea level was 30 mg. per 100 ml. Twelve hours after the last meal control samples of arterial blood and urine were obtained. Chlorothiazide 3 g. (53 mg. per kg. of body-weight) was then given by mouth, and changes in her blood and urine were followed for the next five hours. The patient remained fasting but was encouraged to drink tap-water. The results are shown in fig. 1. There was a slight but definite transient decrease in the pH of her arterial blood, an increase in the pH of her urine, and a sharp rise in the rate of excretion of bicarbonate. The rate of excretion of hydrogen-ion diminished (decrease in titratable acid and disappearance of ammonia), and the rate of

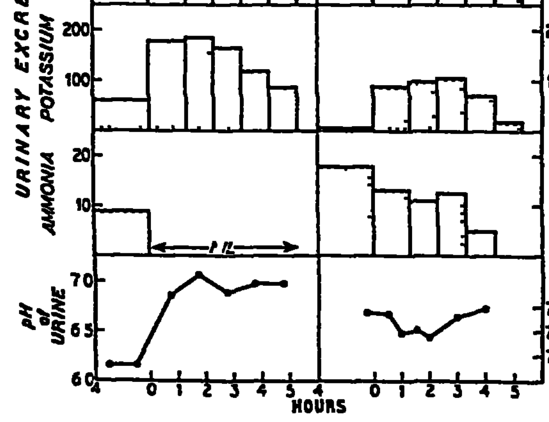

Fig. 1.—Short-term study of effects of a single oral dose of chlorothiazide 3 g. on pH of arterial blood and on volume and composition of urine.

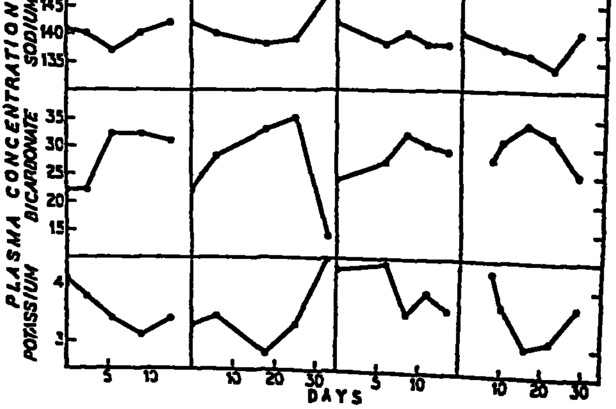

Fig. 3.—Plasma-electrolyte levels during initial period of treatment (cases 1–4).

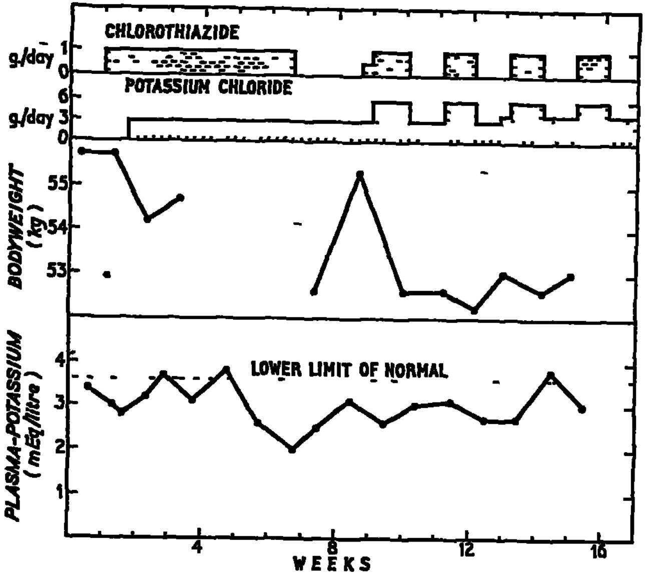

Fig 4—Case 1 (nephrotic syndrome) effect of prolonged intermittent chlorothiazide therapy on body-weight and plasma-potassium level

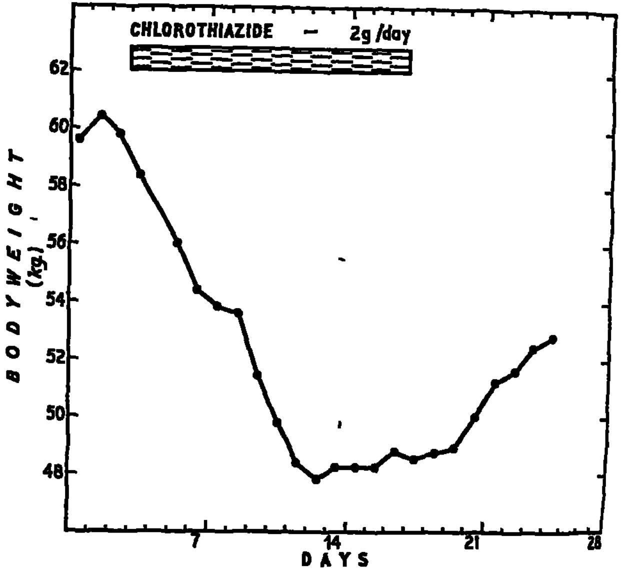

Fig 6—Case 5 (congestive heart-failure) response of body-weight to first course of chlorothiazide

excretion of potassium increased about three-fold These effects can reasonably be attributed to inhibition of renal carbonic anhydrase (Counihan et al 1954) The considerable increase in excretion of chloride is unlike the effects of carbonic anhydrase inhibitors and suggests that chlorothiazide has a separate action similar to that of the organic mercurial diuretics

Nephrotic Syndrome (cases 1–3)

Before receiving chlorothiazide all three patients were œdematous and retaining sodium despite a very low intake When chlorothiazide was given, they had a prompt diuresis with loss of weight and reduction or disappearance of œdema There was a considerable increase in the urinary excretion of sodium and chloride, the average ratio of chloride to sodium in the first six days being 1 18 1 0 (fig 2) In two of the patients this was accompanied by 25–33% increase in urinary output of potassium, in the third patient the urinary excretion of potassium decreased slightly during the first five days but increased later to an average of 27% above the control levels Changes in plasma-electrolyte levels are shown in fig 3

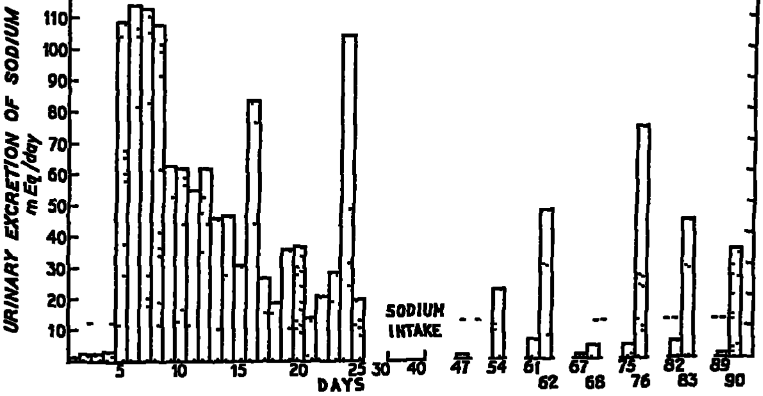

Fig 5—Case 4 (ascites due to portal hypertension) effect of chlorothiazide therapy on body-weight and urinary excretion of sodium Initial response was satisfactory, but after seven weeks patient became resistant to chlorothiazide and mersalyl given separately, although he responded when they were given together

Cases 1 and 2 have now been on treatment with a low-sodium diet and intermittent chlorothiazide for five or six months Œdema is controlled, and the patients feel well, but both have developed persistent hypokalæmia despite oral potassium supplements of up to 80 mEq daily as potassium chloride (fig 4) Studies with an increased sodium diet were made on case 3 in hospital When taking chlorothiazide he could be allowed 44 mEq of sodium daily, but, if the intake was increased to 88 mEq daily, œdema returned. It had been hoped that a diet with a higher sodium content would reduce the tendency to hypokalæmia, but the lowest plasma-potassium level (3 1 mEq per litre) occurred while he was having 88 mEq of sodium (5 1 g of NaCl) daily

During the period of observation the 24-hour urinary output of protein has remained unaltered Cases 1 and 3 had an excess of red blood-cells, white blood-cells, and granular casts in their urine, but repeated Addis counts have not shown any significant change

Specimens of urine from cases 1 and 2 were tested for glucose with glucose-oxidase tape In both patients the control urines gave negative reactions but glucose was found after chlorothiazide had been given In case 3 the glucose content of the urine was measured, during the control period he excreted 2 9–3 9 g daily, and this did not increase during the first fourteen days of chlorothiazide therapy

Cases 1 and 3 had hypertension, this was not affected by chlorothiazide

Ascites and Portal Hypertension (case 4)

This patient had gradually increasing ascites despite restriction of sodium and regular injections of mersalyl In the control period his urinary output of sodium was 1–2 mEq daily, given chlorothiazide he had at first a prompt diuresis with a considerably increased output of sodium and chloride The average urinary chloride to sodium ratio over the first six days was 1 50 1 During the initial eleven days of treatment losses of potassium exceeded the estimated intake by about 330 mEq, and at the end of this time the plasma-potassium level had fallen to 3 0 mEq per litre Subsequent details of this patient are shown in fig 5 He has become refractory to the action of chlorothiazide and to that of mersalyl although he still responds when both drugs are given together Resistant hypokalæmia has developed, but no symptoms can be attributed to it

Congestive Heart-failure

Fig 6 illustrates the dramatic response obtained with chlorothiazide in an old man with congestive heart-failure Rest in bed, a low-sodium diet, and digitalis had not relieved his breathlessness and œdema When he was given chlorothiazide, his general condition and appetite improved, but it was impossible to keep him to a low-sodium diet A steady state was finally achieved with a normal diet without added salt, chlorothiazide 2 g daily, and injections of mersalyl 2 ml twice a week His plasma-potassium level fell to 3 4 mEq per litre, and in a second patient with heart-disease the plasma-potassium level fell to 3 0 mEq per litre after 9 g of chlorothiazide had been given for four days

Discussion

The chief action of chlorothiazide appears to be to cause a rapid increase in the rate of excretion of chloride by the kidneys In this it resembles closely the diuretic action of organic mercurial compounds (Pitts and Sartorius 1950) A different effect, attributable to the inhibition of carbonic anhydrase, can be demonstrated in short-term studies This secondary action may explain why chlorothiazide produces considerable hypokalæmia, although it is unusual for mercurial diuretics to do so

In practice chlorothiazide has proved to be a most effective diuretic agent In two of our patients the diuretic action has continued for five or six months, although a third patient developed resistance in two months Compared with injections of mercurial diuretics, chlorothiazide has the great advantage of being active when taken by mouth. We have no reason to believe that it will be effective given to patients completely resistant to the action of mercurial diuretics, but in this situation a combination of chlorothiazide and mersalyl injections may provoke a diuresis

Mercurial drugs sometimes damage the renal tubules (Preedy and Russell 1953) and are often avoided in patients with renal œdema Chlorothiazide does not contain mercury and may be a safer diuretic agent in this type of case It compares favourably with the other oral diuretic drugs available It is more effective than acetazolamide (' Diamox ') and does not cause gastrointestinal symptoms as does aminometradine (' Mictine ')

Although chlorothiazide is an effective diuretic, a restricted intake of salt will continue to be necessary in many cases Most patients with œdema of renal origin, or with ascites from portal hypertension and liver damage, will continue to require very low sodium diets The intake of salt permissible in patients with cardiac œdema will vary, some will be able to tolerate a diet with " no added salt ', others will have to be restricted to a minimal intake of dietary salt despite the continuous use of chlorothiazide

Chlorothiazide seems to be remarkably well tolerated Gastrointestinal disturbances are unusual, our first patient developed diarrhœa and vomiting when first given chlorothiazide but she had had similar episodes in the past when losing œdema fluid rapidly No changes of the white blood-cells and no sensitivity reactions have been observed

The development of hypokalæmia appears to be by far the most important side-effect of chlorothiazide It is most likely in patients with resistant œdema on a low-salt intake, and, in such cases, even large supplements of potassium chloride may fail to keep the plasma-potassium level normal The dangers of hypokalæmia are difficult to assess We have not met with any clinical features that can be attributed to it Hypokalæmia may potentiate the toxic effects of digitalis on the heart (Lown et al 1951), and this may well prove to be the most serious danger of chlorothiazide therapy The possibility of renal damage due to prolonged depletion of potassium should also be considered (Relman and Schwartz 1956) If a patient has œdema that is persistent enough to need both severe restriction of sodium (44 mEq or less daily) and chlorothiazide therapy (either continuous or intermittent), we would regard it as essential to have regular estimations of plasma-potassium concentrations Initially these should be made at weekly intervals, and suitable supplements of potassium chloride should be given

Summary

A new oral non-mercurial diuretic, chlorothiazide, has been used successfully in patients with the nephrotic syndrome, ascites due to portal hypertension, and congestive heart-failure Two patients with the nephrotic syndrome have now been controlled satisfactorily for five or six months

Chlorothiazide therapy was followed by a considerable and prompt diuresis, with increased excretion of sodium and chloride The mode of action and the therapeutic response resemble those of the mercurial diuretics A subsidiary effect suggesting inhibition of carbonic anhydrase was observed in a short-term study

Chlorothiazide caused hypokalæmia which was difficult to control with oral potassium supplements No other side-effects have so far been observed

We wish to thank Messrs Merck, Sharp & Dohme, Ltd, Hoddesdon, Herts, for supplies of chlorothiazide ('Saluric'), the staff of the routine laboratories of the Courtauld Institute of Biochemistry of the Middlesex Hospital for the plasma-electrolyte estimations, Dr E K Westlake for help with the pH determinations, Mr V K Asta for preparing the figures, and the Clinical Research Committee of the Middlesex Hospital for the provision of laboratory facilities and a personal research grant to J D N N

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" Time was when the clinician could encompass anatomy, physiology and experimental medicine These days have gone Anatomy and physiology, as separate disciplines, have made fantastic progress and, in doing so, have been forced to subdivide into other disciplines Might not the time be opportune for experimental surgery also to prepare itself for the next step in its evolution as a medical science? "—W J DEMPSTER, F R C S, *An Introduction to Experimental Surgical Studies*, p 14 Oxford, 1957

CONTROL OF TREATMENT IN *MYXŒDEMA* BY ELECTROCARDIOGRAPHY

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> The recognition of cardiac symptoms in cases of myxœdema that have gone for long periods without treatment is of great practical importance, for when heart disease is present treatment with thyroid extract must be carried out with great care —
> G R MURRAY, 1897

THIS warning, issued at the outset of thyroid treatment for myxœdema, has been fully justified in the experience of the past sixty years but is still largely ignored It is the purpose of this paper to define the danger of indiscriminate dosage and to show the value of electrocardiography in controlling treatment

It must be assumed that every patient with obvious myxœdema has heart-disease, either from atheroma or from the involvement of the myocardium in the disease itself, hence every patient is in danger from careless treatment Brewer (1951) notes the extreme scarcity of necropsy reports on untreated cases of myxœdema and thinks this is due to the introduction of thyroid treatment in 1891 I doubt if this really explains it, for I am convinced that untreated myxœdema still abounds The twelve cases I am recording represent less than half of the patients I have treated during the past ten years These twelve were typical and recognisable at sight, yet only three had had any previous treatment One of them was interesting in this respect because, although the clinical picture was typical and recognisable, it was not recognised, even in hospital, until the electrocardiogram pointed the way It showed how easily even a typical case may escape recognition unless this possibility is constantly borne in mind

Necropsy records of treated cases, though not plentiful, are readily found Brewer (1951) recorded one, and Smyth (1938) collected five from American literature and records one of his own In every case death was due to acute coronary insufficiency attributed to treatment with thyroid If untreated myxœdema is as prevalent as it seems to be and necropsy records are only to be found in treated cases, it suggests that treatment can be more deadly than the disease

A great difficulty in selecting safe and adequate dosage has been the lack of a reliable means of assessing adequacy Zondek (1918) recorded the typical electrocardiographic changes in myxœdema, but, I believe, this observation has not come into regular use for controlling treatment. This method of control was used in all my cases

The twelve patients in this series all attended my clinic at Torbay Hospital in 1945-57 Only those with a significantly lowered basal metabolic rate (B M R) are included The year of their first visit is noted with their ages in table I Every patient was seen for final assessment in 1957

TABLE I—DOSAGE OF THYROID (GRAINS)

Case no	Sex	Date	Age (yr)	B M R (%) *	Previous thyroid treatment	Daily dose (grains)		Final assessment	
						A	B	Health	Dose
1	M	1947	43	−30	None	1½	2	Good	2
2	F	1954	70	−31	None	1½–6	1	Hypo-thyroid	1
3	M	1952	48	−6	None	¼	½	Very good	½
4	M	1950	55	−37	None	2–½	1½	Fair	1
5	M	1945	56	−25	None for 6 weeks	½	1	Fair	1
6	F	1955	54	−3	None	¼	1½	Fair	1
7	F	1948	51	−11	None	½	2	Good	1½
8	F	1937	31	−15	None for 10 years	2	1½	Fair	2
9	F	1950	38	−28	None for 3 months	½	1½	Fair	1½
10	F	1954	50	−44	None	¼	1½	Very good	1½
11	F	1951	36	−30	None	½	1	Very good	1
12	F	1951	38	−18	None	¼	1	Good	1½

* Before treatment A, Initial B, Maintenance

Electrocardiograms —To simplify the evidence only the standard limb leads are recorded The characteristic feature in myxœdema is flattening or inversion of the T waves in all leads and their rise in response to treatment with thyroid The T-voltage changes are recorded in table II

Dosage —Throughout this paper only the daily total of thyroid extract in grains is noted The initial and maintenance doses in each case are recorded in table I

Case-reports

Case 1 —A man, aged 43, was admitted to hospital on Nov 15, 1947, with painful swellings of his arms, thought to be cellulitis

TABLE II—ANALYSIS OF T-WAVE VOLTAGE IN (MILLIMETRES)

Case no	A			B			C			Dates
	T_1	T_2	T_3	T_1	T_2	T_3	T_1	T_2	T_3	
1	−2 5	−2 5	−1	+2	+2 5	+1	+3 5	+5	+2	A Nov 17, 1947 B Dec 24, 1947 C Mar 3, 1948
2	+1 5	−3 5	−4 5	+1	−1	−2 5	+1	+	+1	A Oct 29, 1954 B Feb 4, 1955 C May 1, 1957
3	+2	+1	−1 5	+3	+4 5	+1 5	+2 5	+2 5	+1	A Aug 29, 1952 B Nov 7, 1952 C Feb 1, 1957
4	−1 5	+1 5	+2 5	−2	±	0	−3 5	+1 5	+5 5	A Mar 11, 1950 B Sept 28, 1950 C Jan 31, 1957
5	+2	−	−3	+3	+	−3	+4	+2	−3	A Nov 24, 1945 B Jan 11, 1946 C Aug 2, 1947
6	−1	−3 5	−1	0	+2	+1 5	0	+1 5	+	A April 3, 1956 B Jan 30, 1957 C June 11, 1957
7	+1 5	+	±	+2 5	+1 5	−	+2 5	+2	−	A Dec 18, 1953 B June 15, 1954 C Feb 6, 1957
8	+1	+2	+	+5	+2 5	−2	+2	+3 5	+1	A July 22, 1950 B Sept 2, 1950 C May 29, 1951
9	+	+2 5	+2	0	+1 5	+1 5	+	+3 5	+3	A Oct 2, 1950 B Jan 31, 1951 C Mar 5, 1957
10	−	0	+	+1 5	+2	+1	+4	+4	+	A June 24, 1954 B Oct 9, 1954 C Jan 11 1957
11	+	0	−	+	+2 5	+2	+3	+4	+1	A Dec 15, 1950 B Mar 16, 1951 C Jan 18, 1957
12	0	−	−	+1 5	−1	−1	+1 5	+	−1 5	A May 14, 1953 B Nov 26, 1953 C Mar 12 1957

A, before treatment, except in case 3 B, first significant voltage change C, final state −, + less than 1 mm 0, isoelectric

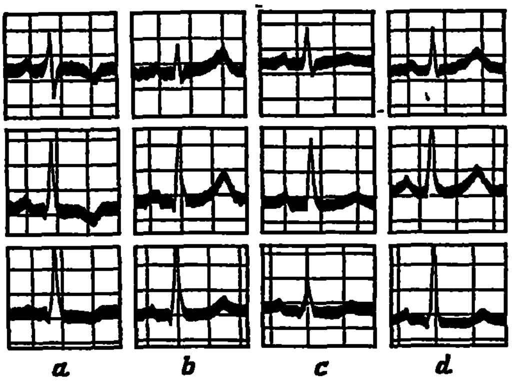

Fig 1—Serial electrocardiograms of case 1 a, Nov 17, 1947 b, March 3, 1948 c, Jan 25, 1957 d, April 11, 1957

He had had some chest pain on exertion, so an electrocardiogram was taken (fig 1*a*) It suggested myxœdema, and in the light of this the clinical picture was seen to be typical The patient was started at once on thyroid gr 1, gradually increased to gr 2 by Jan 7, 1948 The swellings quickly subsided, and by March 3, 1948, the T voltage was fully restored (fig 1*b*) The patient was not seen again for 10 years, when he was sent for on Jan 25, 1957 The painful swellings of his arms had returned, he complained of feeling cold and breathless, and T voltage was reduced (fig 1*c*) He said that 5 years previously the dosage of thyroid was reduced to gr 1 daily because of palpitation He had taken this dose since It was now increased to gr $1^1/_2$, and by April 11, 1957, his arms were normal and T voltage increased (fig 1*d*) He still felt cold and breathless, so the original maintenance dosage of gr 2 daily was restored He has kept well on this since It was remarkable how closely the rise and fall of the T waves corresponded to the disappearance and reappearance of localised patches of myxœdema

Case 2 —A woman, aged 70, was admitted to hospital on Aug 30, 1954, during my absence, with advanced myxœdema She was at once given thyroid gr $1^1/_2$ daily After 10 days this dosage was increased to gr $4^1/_2$, though she had already begun to complain of anginal pain,[9] which she had never had before On Sept 22, 1954, the dosage was increased to gr 6 daily Next day the patient had an attack clinically resembling coronary thrombosis The dosage was reduced to gr 3 daily, and on Sept 28, 1954, treatment with thyroid was stopped On Oct 4, 1954, the patient was still having angina at rest, but there were no signs of heart-failure The electrocardiogram (fig 2*a*) showed T inversion in all leads superimposed on the changes of myocardial ischæmia Treatment with thyroid gr $^1/_4$ daily was started, and increased to gr $^1/_2$ on Oct 11, 1954 She tolerated this, but an electrocardiogram taken 3 weeks later (fig 2*b*) showed that it was inadequate She kept on this dose for about a year, and it was then increased to gr 1 daily She was comfortable with this dose but could not tolerate gr $1^1/_2$ daily, so gr 1 daily was accepted as her maintenance dosage as an inevitable compromise With this she kept reasonably well and could do all that she wanted to When seen again on March 4, 1957, she was obviously hypothyroid, and electrocardiography still showed the typical T inversion (fig 2*c*), but, when the dosage was increased to gr $1^1/_2$ daily, she got more pain She is still taking gr 1 daily

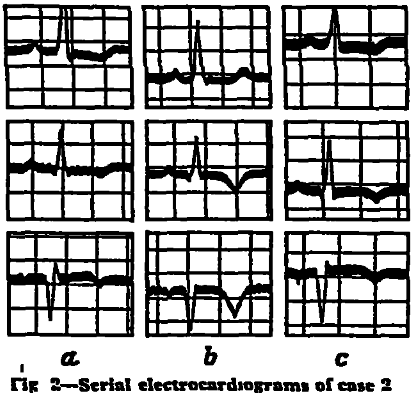

Fig 2—Serial electrocardiograms of case 2 a, Oct 4 1954 b, Oct 29, 1954 c, March 4, 1957

Case 3 —A man, aged 43, underwent in 1947 partial thyroidectomy for thyrotoxicosis with auricular fibrillation After operation normal rhythm was restored, and he was soon leading a very active life as a fruit farmer At the age of 48 he came to see me on Aug 28, 1952, because for the past 2 years he had become increasingly tired and had had three prolonged attacks of tachycardia with general trembling and lately he had been having chest pain on exertion He said that during the past six months he had lost a stone in weight Clinical examination revealed nothing of interest, and his electrocardiogram (fig 3*a*) was passably normal Further investigation revealed that his B.M.R was −6%, basal pulse-rate 56, basal blood-pressure 112/88 mm Hg, and blood-cholesterol level 235 mg per 100 ml On Sept 14, 1952, he was started on thyroid gr $^1/_4$ daily, and by Nov 7, 1952, his electrocardiogram (fig 3*b*) showed a striking rise in T voltage The same dosage was continued, but 2 months later he began to feel tired again, and so it was increased to gr $^1/_2$ daily He has kept quite well on this dosage, doing exceptionally heavy work at times This case shows that a single electrocardiogram may be misleading It was the response of the T waves to thyroid that was pathognomonic

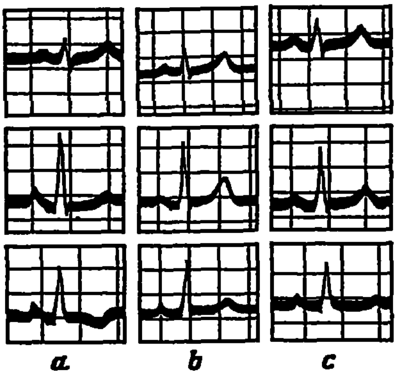

Fig 3—Serial electrocardiograms of case 3 a, Aug 28, 1952 b, Nov 7, 1952: c, Feb 1, 1957

Case 4 —A man, aged 55, was admitted to hospital on March 27, 1950, with advanced myxœdema and a grossly enlarged heart T T D 17 5 cm He was started at once on thyroid extract gr 2 daily 8 days later he had an alarming attack of acute pulmonary œdema The dosage of thyroid was reduced to gr $^1/_2$ daily, and he promptly recovered On May 26, 1950, he was much better, and the size of his heart was normal (total transverse diameter 12 5 cm) The dosage of thyroid was increased to gr 1 daily and 4 months later to gr $1^1/_2$ daily He kept on this dosage for 6 years During this period he had a series of " thrombotic " events, left quadrantic blindness (April 27, 1950), right hemiplegia with aphasia (July 12, 1953), and acute coronary insufficiency (Dec 25, 1956) The coronary attack was short and sharp, with complete recovery after 24 hours The patient was kept in bed for 2 weeks but was afebrile and symptomless The electrocardiograms were obscured by extreme left axis-deviation which persisted after the heart size was restored to normal The day after the coronary attack there was slight R-T deviation in lead 4 The patient has had no anginal pain since and no residual heart weakness After the coronary attack the dosage of thyroid was reduced to gr 1 daily The patient has kept well on this since

Case 5 —A man, aged 56, who had been under treatment for progressive osteo-arthritis since 1933, begin to have angina of effort in February, 1945 In the following September myxœdema was discovered, and he was given thyroid gr 3 daily His anginal pain became worse and now came on at rest, sometimes he had three or four attacks a day About a month after starting treatment with thyroid he had an attack considered to be coronary thrombosis, but no electrocardiogram was taken Thyroid was stopped, and the pain then lessened, but during the next 6 weeks the patient became progressively more myxœdematous On Nov 24, 1945, he was admitted to Torbay Hospital, obviously myxœdematous His B M R was

—25%, and his electrocardiogram showed left axis-deviation with flattening of T_1 and inversion of T_2 He was still having angina of effort On Dec 20, 1945, treatment with thyroid gr 1/2 was started He improved steadily and on Feb 22, 1946, was having no serious pain, but his electrocardiogram 2 weeks later showed little change The dosage of thyroid was increased to gr 1 daily, which he tolerated quite well Because of distortion by left axis-deviation the electrocardiogram was difficult to interpret; so on April 22, 1946, his B M R was estimated again, and found to be —16% The dosage of thyroid was gradually increased to gr 2 by Jan 4, 1947 On April 19, 1947, the B M R was +7%, but he was having a lot of anginal pain, so the dosage was reduced to gr 1 1/2 daily At his last visit, on Aug 2, 1947, he was still complaining of pain, though the T voltage was much improved (table II) He was advised to revert to thyroid gr 1 daily He then left the district On Jan 21, 1957, his doctor reported that he was still on the same dosage of thyroid, and was getting some effort pain, but his chief trouble was the arthritis

Case 6—This case illustrates a special risk from overdosage with thyroid in *myxœdema secondary to thyroidectomy* A woman, aged 54, was admitted to hospital on Jan 9, 1956, with a large toxic goitre She had been fibrillating for about a year but had no obvious signs of heart-failure Her B M R was +43% She underwent complete thyroidectomy on Jan 17, 1956, followed by a full course of radiotherapy because the goitre was malignant On March 28, 1956, her appearance and behaviour suggested myxœdema, her B M R was —3%, and her electrocardiogram showed inversion of T in all leads Treatment with thyroid gr 1/4 daily was started on April 2, 1956, and increased to gr 1/2 daily on Aug 29, 1956 Her principal symptom was depression, which was improving slowly but steadily On Oct 31, 1956, the dosage of thyroid was increased to gr 1 daily 3 months later the depression had passed and the electrocardiogram showed considerable improvement in T voltage, but the P–R conduction time was 0 24 sec, and the patient felt cold and was breathless on hills The dosage of thyroid was increased to gr 1 1/2 daily and a month later to gr 2 daily 2 months later she felt well but was fibrillating Treatment with thyroid was stopped, and quinidine was given, which converted the fibrillation to flutter In spite of full digitalisation, which induced nausea and vomiting, the flutter persisted, though at a slower ventricular rate It seemed likely that the myocardium was damaged, so it was decided to let the flutter be and to control the ventricular rate with minimal doses of digitalis In retrospect one can see that it would have been wiser to keep the thyroid dosage at gr 1 daily, but at the time I thought her thyroid had been so thoroughly destroyed that she might need a larger dose than usual

Discussion

Sensitivity to Thyroid

It is known that patients with myxœdema are apt to be hypersensitive to thyroid extract, the more advanced the disease the greater is this tendency This sensitivity is expressed as anginal pain In the angina of myxœdema the pattern of pain may be confused by treatment Before treatment it usually appears as an effort pain, which subsides as treatment becomes effective After treatment there may be added a pain with distinctive qualities which is aggravated by treatment Seven of my patients had angina of effort relieved by treatment Two of them (cases 2 and 5), after treatment had started, had spasms of pain at rest, sometimes three or four attacks a day, usually of short duration but sometimes lasting several hours This pain was not relieved by trinitrin and was aggravated by thyroid Both of these patients had started with grossly excessive dosage, and both of them had attacks indistinguishable clinically from coronary thrombosis But in these attacks, though the pain was severe, collapse was minimal, and the attacks subsided quickly when treatment with thyroid was stopped, leaving little evidence of persistent myocardial damage

The most favoured explanation of these coronary attacks following treatment is that they are due to a relative vascular insufficiency induced by a rise in the metabolic rate It is difficult to reconcile this theory with the typical lability of the attacks, which may come and go several times in a day, moreover it is inconsistent with an experience recorded by Oliver and Boyd (1957), who used the acetyl analogue of triiodothyronine to reduce cholesterinæmia in a group of twelve men with known coronary disease Two of them had severe angina of effort during this treatment, although the B M R was not raised

A notable feature in the necropsies referred to above was myocardial infarction without thrombosis Brewer's (1951) patient died suddenly in a manner suggesting coronary thrombosis, but no thrombus was found, Smyth (1938) records a case in which a large area of necrosis was found in the myocardium without any evidence of thrombosis He also says that, in three of the five other necropsies reviewed by him, on patients who had met a coronary death while under treatment, no thrombus was found Wood (1956) refers to myocardial infarction without thrombosis as occurring in myxœdema when treated too vigorously with thyroxine If these anginal crises and sudden deaths under treatment are sensitivity reactions, this could explain the capricious nature of the angina and infarction without thrombosis, because one can readily associate such coronary sensitivity with reversible occlusion in terms of intimal swelling and vasospasm

The Electrocardiograms

On the whole the behaviour of the T wave fulfilled expectation When the electrocardiogram is distorted by coronary disease, as in case 2, or by extreme axis-deviation, as in cases 4 and 5, it is not easy at first to recognise the T-wave changes of myxœdema, but in serial electrocardiograms these were recognisable in all cases When the electrocardiogram is not distorted, the changes induced by myxœdema may be pathognomonic, but what clinches the diagnosis is the response of the T-waves to thyroid The chief value of the electrocardiogram is in the control of treatment, because by its use one can judge the adequacy of dosage

Dosage of Thyroid

Initial dosage—After my experience in case 4, when gr 2 induced acute ventricular failure, I decided to use gr 1/4 as a standard initial dose This later proved to be adequate, even in case 10, whose R M R was the lowest of the series When the change in T voltage (table II) was effected, she was still on gr 1/4 daily In Brewer's (1951) case sudden death followed an initial dose of gr 3/4 If gr 1/4 is adequate, there is no reason for starting with more

Maintenance dosage—This was the dosage reached when symptoms had cleared and T voltage was fully restored From these results it seems to be rarely necessary to give more than gr 2 daily for maintenance In this series the thyroid needs bore no relation to the B M R In case 10, with the lowest B M R, the maintenance dosage was only gr 1/2 whereas in case 8, in which the B M R was only —15%, gr 2 daily was needed to keep her free from symptoms

Final Assessment

Every patient was re-examined in 1957 Three of them were hypothyroid In two of these (cases 1 and 9) the maintenance dosage had been reduced, both of them improved promptly when the original maintenance dosage was restored The other patient (case 2) cannot tolerate an adequate dosage and is still hypothyroid The prominent symptoms in these hypothyroid cases was feeling cold and breathlessness This cold feeling was a well-defined symptom, the patients never felt warm, even in bed it is usually an early symptom and is the last to go Breathlessness was prominent in most of the patients before to develop after immoderate consumption of alcohol and can also be caused by numerous chemical poisons (Sheehan and Moore 1952) Cortical necrosis was suspected clinically in this patient and confirmed post mortem

Drugs

Our only experience of acute renal failure after drug administration has been with the sulphonamide group These are known to give rise to renal failure from obstruction by crystalline deposits and epithelial debris in the urinary pathways and from hypersensitivity lesions in the kidneys, particularly acute tubular necrosis and renal arteritis

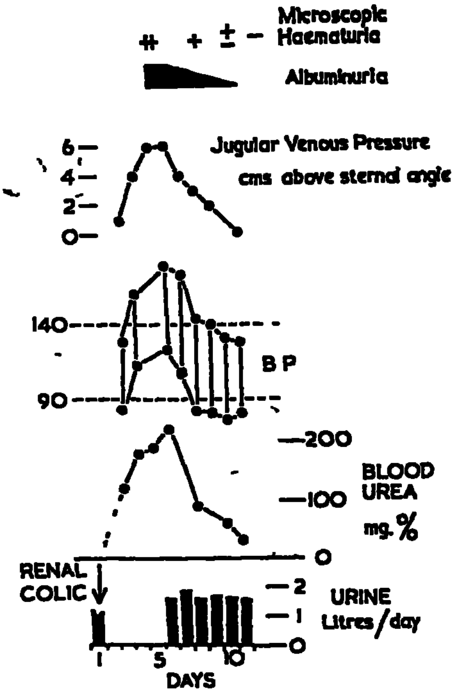

Fig 2—Case 9 rise in blood-pressure and venous pressure probably due to overloading with water and salt during anuria due to sulphonamide obstruction On the 13th day the effective renal plasma flow (p-aminohippurate clearance) was 601 ml per min and the glomerular filtration-rate (thiosulphate clearance) 93 ml per min

Sulphonamide Obstructive Anuria

We have seen a good many cases of sulphonamide crystalluria with hæmaturia and renal colic Only 5 patients, however, had anuria of any note (cases 9–13 and fig 2) 1 patient developed cystitis following urethral catheterisation and, when cystoscopy was done, the ureteric orifices could not be located and the cystoscope was pushed through the friable bladder wall The patient was moribund from peritonitis when we saw him The 4 other patients appeared to have spontaneous diureses When diuresis appeared to start after unsuccessful attempts at ureteric catheterisation, it was our impression that this was due to the moving about of the patient on the journey to the theatre Kolff (1955) emphasises that a rough trip in an ambulance is a good therapeutic measure for such patients Our present policy is to treat conservatively and to avoid urological manipulations Hopper and Partridge (1950) point out that in 82 out of 84 collected cases of sulphonamide obstructive anuria the patients recovered The average onset of diuresis was at 3 1 days and the range was from one to eleven days

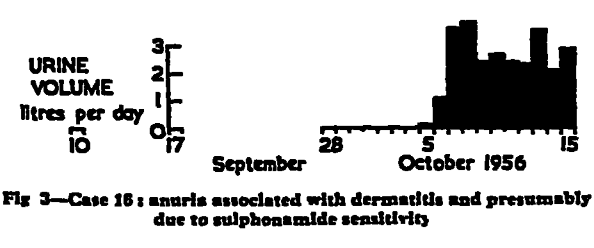

Fig 3—Case 16: anuria associated with dermatitis and presumably due to sulphonamide sensitivity

Sulphonamide-sensitivity Anuria

3 patients developed acute renal failure apparently as a sensitivity reaction to sulphonamide drugs (cases 14–16 and fig 3) They all had associated dermatitis, and in 1 case this started after exposure to the sun The renal failure was more severe, and the anuria of longer duration, than in sulphonamide obstructive anuria 2 patients recovered on conservative management The 3rd patient died partly from rather poor management of the anuria and partly from pyelonephritis superimposed on the tubular necrosis and possibly due to ureteric catheterisation

Renal failure due to potentially hæmolytic drugs—e g, quinine and mephenesin—has been discussed in a previous paper on anuria following intravascular hæmolysis (Bull et al 1957)

Anuria has been noted to follow exposure of the kidney to radio-opaque material—e g, in aortography (Dormandy et al 1957) and in retrograde pyelography with pyelorenal backflow (Grieve and Lowe 1955)—but these complications are rare

Discussion

The pattern of disturbed renal function in our cases of acute tubular necrosis due to poisoning and to sulphonamide sensitivity was the same as in our cases of concealed accidental hæmorrhage, intravascular hæmolysis, and criminal abortion, which are the other most common causes of acute tubular necrosis in our series Despite the varying histological pictures and different types of tubular damage described by Oliver et al (1951) we have failed to show any functional differentiation between cases of tubular necrosis due predominantly to nephrotoxins and cases due predominantly to renal ischæmia (Bull et al 1950, Lowe et al 1954, Emslie-Smith et al 1956) As regards sulphonamide obstructive anuria we have studied renal function in only 1 case (case 9), in which there was a much earlier recovery of function than would be expected in tubular necrosis (fig 2)

Acute renal failure due to poisonings and sulphonamide (either obstruction or sensitivity) should carry a high recovery-rate with adequate treatment. The 2 deaths among our sulphonamide cases were probably avoidable In mercury poisoning there is very extensive tubular necrosis (Allen 1951), but its reversibility is shown by the excellent recovery made by our 3 patients The death due to hydrochloric-acid poisoning was due to associated damage of the respiratory and alimentary tracts, renal failure being incidental, and the death due to oxalic-acid poisoning was unexplained and took place when the patient was in the recovery phase of the renal lesion Our cases of phenol poisoning have been mild, and we have not encountered a fatal case

Summary

Of 5 cases of acute tubular necrosis due to poisons 3 were due to mercury and 1 each to oxalic and hydrochloric acids The patients with mercurial tubular necrosis recovered, but the 2 others died Only very mild cases of phenol and turpentine poisoning were encountered, and none of the patients had anuria. 2 chronic alcoholics died in renal failure after drinking bouts one had lobar pneumonia and acute tubular necrosis, the other had renal

cortical necrosis There were 5 cases of sulphonamide obstructive anuria and 3 of sulphonamide sensitivity with renal failure, 1 patient in each group died

Appendix

Case 1 —A woman, aged 36, was prescribed mercuric-chloride tablets for use in vaginal douching for vaginitis She used too concentrated a solution and developed a severe vaginal irritation with vomiting, diarrhœa, and a brisk diuresis that was followed within a few hours by anuria Dimercaprol was not given until the fourth day of anuria She was treated by the intragastric regime (Bull et al 1949) and with the artificial kidney on the tenth day of anuria Her blood-urea level rose to a maximum of 325 mg per 100 ml, and diuresis developed on the twelfth day She made a good clinical recovery

Case 2 —A woman, aged 21, swallowed some mercuric oxide in a suicidal attempt Faintness, vomiting, and anuria followed She was treated with gastric lavage but had no dimercaprol Anuria persisted for eleven days, and her maximal blood-urea level was 380 mg per 100 ml She was treated conservatively by the intragastric regime and made a good clinical recovery Convalescence was delayed by disturbance of her central nervous system in the early and late diuretic phases The chief features were tremor, ataxia, and dysarthria of the type seen in industrial mercury poisoning Her incoordination is evident from her handwriting (fig 1)

Case 3 —A woman, aged 23, swallowed some "hair-curling tonic" (which contained mercuric chloride 24 g per packet) She collapsed with immediate abdominal pain and was taken to hospital, where her stomach was washed out She had bloody diarrhœa, vomiting, and anuria Dimercaprol was not given until the second day With careful conservative management she made a good recovery after eight days' anuria

Case 4 —A woman, aged 30, was admitted to hospital some hours after swallowing a teaspoonful of oxalic-acid crystals Her stomach was washed out, and she had an intravenous infusion of noradrenaline in physiological saline solution for shock She had anuria and then severe oliguria, and her blood-urea level rose to 450 mg per 100 ml on the sixteenth day Thereafter she entered the early diuretic phase, and her blood-urea level began to fall Treatment was by intravenous infusion of hypertonic glucose into the inferior vena cava and with retention enemata of sodium-charged cation-exchange resin Unfortunately she had an unexplained profound circulatory collapse on the twenty-second day and died Necropsy confirmed the diagnosis of acute tubular necrosis

Case 5 —A man, aged 54, was admitted to hospital some hours after swallowing an unknown quantity of hydrochloric acid in a suicidal attempt On admission emergency tracheotomy was done for laryngeal obstruction due to œdema He was very restless and had gross excoriation in the mouth and generalised râles in the lungs His blood-pressure was 120/90 mm Hg Since he did not pass urine that day he was catheterised at night, 300 ml of dark brown urine was obtained, and its specific gravity was 1 020 Only small quantities were obtained by catheter from that time until death forty-eight hours later, the total amounting to 200 ml The urine was dark, of specific gravity 1 010, and contained pigmented casts The blood-pressure remained between 110/70 and 140/90 mm Hg until shortly before death At necropsy there were gross signs of acid erosion in the air passages and upper gastro-intestinal tract, pulmonary œdema, and bronchopneumonia Histologically the kidneys showed acute tubular necrosis, with a few pigment casts in the collecting tubules

Case 6 —A woman, aged 61, drank half a cupful of 'Lysol' in a suicidal attempt She was found unconscious and was brought into hospital, where she recovered consciousness rapidly Her general condition was good, her blood-pressure was 145/70 mm Hg, and there were brownish staining on her chin and ulceration in her mouth The first samples of urine showed carboluria and were well concentrated (urinary urea 1800–3200 mg per 100 ml) Treatment consisted of olive oil orally, prophylactic penicillin, and careful water and electrolyte balance Urine volume was on the low side for a few days, the blood-urea level fell from 60 mg per 100 ml on the second day to 20 mg per 100 ml on the fifth day She recovered quickly

Case 7 —A man, aged 42, was found semiconscious in his house and brought into hospital He had been a very heavy drinker for years and had been indulging excessively during the past month He had had some pain in his left chest for forty-eight hours On examination he was drowsy and breathless, his blood-pressure was 80/50 mm Hg, and there were signs of left lower lobar pneumonia He passed 180 ml of urine on the first day There was heavy proteinuria, and many red cells and a few granular and cellular casts were seen microscopically in the spun deposit He remained severely oliguric, and his blood-urea level rose from 96 mg per 100 ml on the second day to 496 mg per 100 ml on the seventh day in hospital He died on the eighth day Necropsy showed resolving left lower lobar pneumonia, pulmonary œdema, and several hæmorrhages into the trunk muscles The kidneys showed typical lesions of acute tubular necrosis affecting the distal nephrons and severe hydropic swelling of the proximal tubular cells There was also very mild glomerulitis

Case 8.—A man, aged 27, was found unconscious in a chemist's shop and brought into hospital He had been drinking heavily for some months and had consumed a bottle of whisky during the previous day Examination of the cerebrospinal fluid and radiography of the skull were normal He recovered consciousness but was hallucinated and required sedation with paraldehyde Despite good general condition and a blood-pressure of 124/64 mm Hg he had very severe oliguria, with red cells and hyaline and granular casts in his urine He developed epileptiform fits, and his blood-urea level rose to 155 mg per 100 ml on the third hospital day, when he died Necropsy confirmed the clinical diagnosis of renal cortical necrosis

Case 9 —A man, aged 34, had 30 g of sulphadiazine during outpatient treatment of gonorrhœa He developed renal colic, hæmaturia, and then anuria Two attempts at ureteric catheterisation, one under spinal anæsthesia, failed, and after two days' anuria he was transferred to our care He had been grossly overloaded with salt and water and had developed hypertension, increased jugular venous pressure, basal crepitations in the lungs, and œdema On the fourth day he was cystoscoped under local anæsthesia His bladder mucosa was injected and œdematous A ureteric catheter was passed a few centimetres up the left ureter, and some epithelial debris was removed No crystals were seen microscopically In the next twelve hours he passed 275 ml urine and subsequently he made a good clinical recovery Data are shown in fig 2 Note that renal function tests on the thirteenth day were near the lower limit of normal

Case 10 —A man, aged 25, had a vague illness characterised by anorexia, vomiting, and abdominal pain He received sulphadiazine 20 g in four days and on the fourth day developed hæmaturia and oliguria He was admitted to hospital and in the next four days passed only 275 ml of bloodstained urine He was transferred to our care, and on the fifth day of anuria cystoscopy was done under low spinal anæsthesia His bladder mucosa was œdematous, and the ureteric orifices were not located On return to the ward he started to pass urine, and in the next twelve hours 4200 ml was recovered His highest blood-urea level was 93 mg per 100 ml on the fifth day He made a good clinical recovery

Case 11 —A man, aged 63, was treated with sulphamezathine 24 g in four days for a chest infection and on the fourth day developed loin pain, hæmaturia, oliguria, and then anuria He was admitted to hospital next day, where bladder catheterisation confirmed anuria He was cystoscoped two days later, but the procedure was abandoned after the patient developed severe shock The cystoscope had perforated the œdematous inflamed bladder wall, but this fact was not appreciated at the time Paralytic ileus developed, and he was transferred to our care He died on the sixth day of anuria Necropsy showed peritonitis due to traumatic perforation of the bladder wall

Case 12 —A man, aged 45, was treated with sulphamezathine 12 g for tonsillitis and then developed renal colic, hæmaturia, and then anuria An attempt at ureteric catheterisation failed on the fifth day, and he was transferred to our care Spontaneous diuresis developed on the sixth day, however, and he made a good clinical recovery His highest blood-urea level was 130 mg per 100 ml on the fifth day

Case 13 —A woman, aged 42, was treated for a chest infection with sulphamezathine 19 g in three days She then developed renal colic, hæmaturia, and anuria She remained anuric for three days and then had a rather gradual diuresis Her highest blood-urea level was 106 mg per 100 ml on the fifth day

Case 14 —A woman, aged 54, was treated with 12 g of a sulphonamide drug (the exact preparation was unknown) for an upper respiratory infection She developed a skin rash and oliguria, and the drug was stopped She was admitted to hospital three days later and was treated with alkalis and intravenous fluids Ureteric catheters were passed and the renal pelves washed out with bicarbonate solution There was no evidence of ureteric obstruction, and no crystalluria was evident On the eighth day of anuria she was transferred to our care She was drowsy and œdematous and had bronchopneumonia and severe dermatitis She died on the tenth day Necropsy showed staphylococcal bronchopneumonia, acute tubular necrosis, pyelonephritis, and multiple abscesses in the left kidney Tubular necrosis was considered to be due to sulphonamide sensitivity, and the pyelonephritis and renal abscesses were thought to be superimposed lesions due to infection following ureteric catheterisation

Case 15 —A man, aged 65, was treated with phthalylsulphathiazole preoperatively for rectal carcinoma Dermatitis and oliguria developed Cystoscopy was performed , only the right ureter could be catheterised, and no abnormality was found The blood-urea level, which had been 25 mg per 100 ml on admission, rose to 254 mg per 100 ml , and then with spontaneous diuresis, fell to 74 mg per 100 ml At this time the patient's general condition was fair, and he had an exacerbation of chest infection Palliative colostomy was done after preparation with blood-transfusion and breathing exercises

Case 16 —A woman, aged 62, developed diarrhœa, and after eight days she consulted her doctor, who prescribed sulphaguanidine Next day severe dermatitis began while she was sitting in the sunlight The rash spread, and the drug was stopped after three days Two days later left basal pneumonia developed, and was treated with erythromycin On the twelfth day after starting drug therapy she had anuria, and on the sixth day of anuria she was admitted to hospital Diuresis began two days later, and her blood-urea level fell rapidly from its highest level of 230 mg per 100 ml (fig 3) No crystals were present in freshly voided urine at the onset of diuresis In the early diuretic phase there were poor concentration of urine and failure of conservation of sodium and potassium On the twelfth day after onset of diuresis a water load of 1 litre led to a maximal flow of 9 ml of urine a minute, which was reduced to 1 ml a minute after the intramuscular injection of 5 units of posterior pituitary extract, thereby showing the return of tubular function Patch-testing during convalescence confirmed sulphonamide sensitivity The patient's daughter, like her mother, developed an acute skin eruption after treatment with sulphonamide , neither had been treated before with sulphonamide

We are grateful to Dr Robert Semple for permission to include case 8

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AN ATYPICAL CARCINOID TUMOUR SECRETING 5-HYDROXYTRYPTOPHAN

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THE syndrome associated with metastasising argentaffinoma has now been well documented, and it seems likely that many of the manifestations are due to an excess of 5-hydroxytryptamine elaborated by the tumour Among the many cases published, a few, including the third patient described by Snow et al (1955), present certain atypical features Prompted by the similarity to another atypical patient described by Smith et al (1957), we have reinvestigated this patient Our findings suggest that he may belong to a distinct clinical group in which the tumours produce 5-hydroxytryptophan instead of 5-hydroxytryptamine

Case-report

A detailed clinical description of this man, aged 45, has already been published (Snow et al 1955) To summarise, flushing attacks precipitated by food and particularly by alcohol had been present for more than twenty years The flush was patchy and bright red, and could be attenuated by anti-histamine therapy Diarrhœa had never been a feature The patient was first observed four years ago, when his hard enlarged palpable liver was found at laparotomy to be full of metastases from a small primary tumour in his stomach The hepatic enlargement has remained unchanged up to now, and there has been no deterioration in his general condition, which remains excellent His main complaint continues to be of intermittent attacks of pain caused by a duodenal ulcer, whose presence was confirmed at the laparotomy Additional radiological investigations since the previous report on this patient have included intravenous pyelography and a skeletal survey, neither of which has revealed any abnormality

Further Investigations

Methods

Urinary 5-hydroxytryptamine was estimated in our respective laboratories either by the colorimetric method of Udenfriend et al (1955b) or by the same 1-nitroso-2-naphthol colour reaction after adsorption on a column of 'Amberlite IRC 50' and elution with sulphuric acid, a standard being carried through the whole procedure The results obtained by the two methods were in close agreement Urinary 5-hydroxyindoleacetic acid was estimated by the method of Udenfriend et al (1955a) or by the method of Macfarlane et al (1956), both of which gave comparable results "Total 5-hydroxyindoles" were measured as the colour reaction produced by 1-nitroso-2-naphthol with the unextracted urine with 5-hydroxyindoleacetic-acid standards Chromatography of the

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TABLE I—PARTITION OF 5-HYDROXYINDOLES IN URINE FROM BLADDER

Specimen no	1		2		3
—	mg per g of creatinine	mg per 24 hr	mg per g of creatinine	mg per 24 hr	mg per g of creatinine
"Total 5-hydroxyindoles"	110	110	99 4	117 0	98
5-Hydroxytryptamine	18	18	20 4	24 0	20
5-Hydroxyindoleacetic acid	43	43	50 3	59 4	47
Balance = 5-hydroxytryptophan	49	49	28 7	33 6	31

urine for indoles was kindly carried out by Dr C E Dalgliesh (Dalgliesh 1955, 1956) Indole chromatography was also done by the method of Jepson (1955) on ultrafiltered desalted serum and on urine The presence of 5-hydroxytryptamine on chromatograms was confirmed by the method of Jepson and Stevens (1953)

This histamine content of the urine was kindly estimated by Dr R S Stacey, using the method described by Roberts and Adam (1950)

Chromatography

Chromatographic examination was carried out on bladder urine and on separate specimens obtained from each ureter 5-Hydroxytryptophan was present in all the specimens, and 5-hydroxytryptamine, 5-hydroxyindoleacetic acid, and unknown slow-running Ehrlich-reacting spots, presumed to be conjugates, were also found in bladder urine There were insufficient 5-hydroxyindoles in the serum to show on the chromatogram Indole chromatograms were also prepared from the urine of six healthy people who had been given DL-5-hydroxytryptophan intravenously during another investigation (Pare and Sandler, to be published) Apart from an absence of conjugates, these were strikingly similar to those obtained from our patient's urine

Quantitative excretion of 5-hydroxyindoles—Bladder specimens of urine recently obtained and submitted to quantitative partition of 5-hydroxyindoles gave the results shown in table I The 5-hydroxyindoleacetic acid excreted by this patient has been determined on numerous occasions and is fairly constant at 40–50 *mg* per g of creatinine or 40–60 *mg* per twenty-four hours The amount of 5-hydroxytryptamine excreted has been determined chemically on several occasions and agrees fairly closely with that originally determined pharmacologically (Snow et al 1955) If the sum of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid is subtracted from the " total 5-hydroxyindoles ", the result is a function of the level of 5-hydroxytryptophan (Udenfriend et al 1957) and can be used as such for comparing different specimens

Ureteric specimens of urine from right and left ureters are compared in table II as regards partition of 5-hydroxyindoles

TABLE II—PARTITION OF 5-HYDROXYINDOLES IN URINE FROM URETERS

—	mg per g of creatinine	
	Lt ureter	Rt ureter
" 'Total 5-hydroxyindoles '	80 0	81 0
5-hydroxytryptamine	13 0	10 8
5-hydroxyindoleacetic acid	7 8	12 4
Balance = 5-hydroxytryptophan	59 2	57 8

Excretion of Histamine

From examination of an isolated specimen histamine excretion had previously been stated to be within normal limits (Snow et al 1955), but further estimations have repeatedly revealed a high output, 480–940 μg per twenty-four hours, the normal range being 18–62 μg (Roberts and Adam 1950)

Discussion

Enough cases of argentaffinoma syndrome have now been published for a fairly constant clinical picture to emerge which, broadly, varies directly in severity with the mass of tumour present It has been presumed, from the high level of 5-hydroxytryptamine found in the tumour, that this substance is liberated into the blood-stream Certainly the urinary 5-hydroxyindole pattern produced after the experimental injection of 5-hydroxytryptamine (Erspamer 1956) resembles that found in the argentaffinoma syndrome—i e, a large excess of the metabolite 5-hydroxyindoleacetic acid with only a small increase in 5-hydroxytryptamine

When our patient was first described (Snow et al 1955), a large urinary excretion of 5-hydroxytryptamine and a comparatively small one of 5-hydroxyindoleacetic acid were noted, together with other anomalies, for which at that time there was no obvious explanation Recently, however, Smith et al (1957), found in a patient with the carcinoid syndrome a large urinary excretion of 5-hydroxytryptamine and of 5-hydroxytryptophan, its precursor This aminoacid, derived from dietary tryptophan, had not previously been found in other than trace amounts, and it was postulated that renal metastases were secreting intermediary metabolites direct into the urine The intravenous pyelogram was considered to support this view, but Dick et al (1957), in a further report on the same patient, state that retrograde pyelography showed no abnormality

Since our patient also had a large urinary output of 5-hydroxytryptamine, urinary chromatography was carried out, whereupon large amounts of 5-hydroxytryptophan were found as well as 5-hydroxytryptamine and 5-hydroxyindoleacetic acid Intravenous pyelography did not reveal any obvious renal metastases in our patient, however, so ureteric catheterisation was done in an attempt to locate the fault, urine being collected from each ureter separately Indole partitioning gave similar results in both specimens, and, unless bilateral metastases of equal mass were present, which was unlikely, the explanation advanced by Smith et al (1957) cannot apply to our patient

Although Dick et al (1957) estimated the 5-hydroxyindoleacetic acid in ureteric specimens from their patient they took no account of possible differences in urine flow by relating the level of 5-hydroxyindoleacetic acid to that of creatinine The difference they found between the two specimens may therefore not be significant

Chromatograms of our patient's urine bore a striking resemblance to those obtained from urine passed after intravenous injection of 5-hydroxytryptophan into six normal subjects It therefore seemed likely that the principal metabolite of the tumour was 5-hydroxytryptophan, which, when released into the blood-stream, was decarboxylated to 5-hydroxytryptamine elsewhere 5-hydroxytryptophan-decarboxylase activity is known to be widespread (Gaddum and Giarman 1956), and since the level of 5-hydroxytryptophan decarboxylase is especially high in the kidneys (Clark et al 1954), the large output of 5-hydroxytryptamine could be due to direct decarboxylation there 5-Hydroxytryptophan which reached the kidney and escaped decarboxylation would pass unchanged into the urine, and the other major indole fraction, 5-hydroxyindoleacetic acid, would arise from 5-hydroxytryptophan decarboxylated at extrarenal sites and further

TABLE III—RELEVANT CLINICAL AND BIOCHEMICAL FEATURES OF THREE ATYPICAL CASES COMPARED AND CONTRASTED WITH "TYPICAL ARGENTAFFINOMA"

—	Present case	Case of Smith et al (1957)	Case of Waldenström et al (1956)	Typical argentaffinoma
Histology	Atypical, no argentaffin granules	Atypical, no argentaffin granules	Atypical, no argentafin granules	Characteristic argentaffin granules
Distribution of metastases	Mainly hepatic	Hepatic and osseous	Hepatic and osseous	Hepatic
Type of flushes	Bright-red histamine type'	Not discussed in detail	Bright-red histamine type'	Mixed cyanosis erythema, and pallor
Excretion of histamine	Great increase	Great increase	Great increase	Slight increase
Urinary 5-hydroxytryptophan (chromatographic)	Present	Present	Not stated	Absent
Urinary 5-hydroxytryptamine	Great increase	Great increase	Great increase	Slight increase
5-Hydroxytryptamine in tumour	Small amounts	High level	Not stated	High level

metabolised by monoamine oxidase The presence of relatively greater amounts of 5-hydroxytryptophan in the ureteric specimens is compatible with a sudden release of large quantities of it in response to an agent used for inducing or for maintaining general anæsthesia, during which striking and prolonged flushing was noted

It was originally reported that, although tumour tissue from our patient undoubtedly resembled that of a carcinoid tumour, no typical argentaffin granules were found (Prof A C P Campbell) Jacobson (1954) has emphasised the distinction, based on differential staining, between granular argentaffin cells (found in typical argentaffinomata) and argyrophil cells, which have no granules Dr Jacobson kindly examined material from our patient and reported that all the cells were argyrophil This finding fits in well with the site of the primary tumour in the stomach, where argyrophil cells are numerous but argentaffin cells less common

It is obviously tempting to suggest that argyrophil cells may form 5-hydroxytryptophan, whereas argentaffin cells, tumours of which are known to contain 5-hydroxytryptophan decarboxylase (Langemann 1956, Giarman et al 1957), form 5-hydroxytryptamine, but investigation of such a hypothesis will have to await the availability of more tumour tissue There is no inherent improbability, however, in the idea that each type of cell may have a different function, and that tumours may contain different proportions of each A precedent for a tumour with two distinct secretions has already been established in the phæochromocytoma, which may produce different amounts of noradrenaline and adrenaline This hypothesis may explain the high levels of 5-hydroxytryptamine in tumour tissue of the otherwise similar patient of Smith et al (1957), compared with the very low level of 5-hydroxytryptamine in tumour tissue of our patient

Another patient, having features in common with both our own and Smith's patient, was described by Waldenstrom et al (1956) Although the urinary indole chromatographic pattern was not described, higher levels of urinary 5-hydroxytryptamine were obtained by pharmacological assay than in any of the large number of patients with argentaffinoma investigated by these workers (Pernow and Waldenstrom 1957) Other atypical features suggesting the possible clinical identity of these three patients are shown in table III

Neither Smith et al (1957) nor Dick et al (1957) give a detailed clinical description of the flushing attacks in their patient, but the atypical bright-red persistent flush of ' geographical ' pattern reported by Waldenstrom et al (1956) and also seen in our patient, which could be attenuated by anti-histamine therapy, correlates well with the enormous output of urinary histamine in all three patients 5-Hydroxytryptamine is a mild histamine liberator (Feldberg and Smith 1953), so it is not surprising that several patients with the typical argentaffinoma syndrome had an increased output of histamine (Pernow and Waldenstrom 1957), but usually the levels attained are lower than those found in the three patients under discussion

It is improbable that the tumour produces histamine, and Waldenstrom et al (1956) did not detect any in biopsy material from their patient We found no direct histamine-releasing action of 5-hydroxytryptophan on intradermal injection in normal subjects (unpublished observation), but widespread peripheral production of 5-hydroxytryptamine resulting from the excess 5-hydroxytryptophan may have a more pronounced histamine-releasing effect than have the relatively small amounts of free plasma-5-hydroxytryptamine in the typical syndrome

We suggest that the anomalous findings in the three patients discussed can best be explained by the existence of a distinct clinical group of tumours producing 5-hydroxytryptophan

Summary

A patient with the carcinoid syndrome having many atypical features, including urinary excretion of 5-hydroxytryptophan, is described

It is suggested that this case and two others published, form a new clinical group of tumours which secrete 5-hydroxytryptophan

We wish to thank Dr H T Howat for permission to investigate this patient, Mr M Bell, of the clinical laboratory, Manchester Royal Infirmary, for some of the 5-hydroxyindole estimations, Miss Lilith Emslie for expert technical assistance, and the Royal Free Hospital Endowment Fund for defraying her salary, Dr D N Baron and Dr D A K Black for helpful criticism, and Prof K R Hill for providing facilities

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INFLUENZAL ENCEPHALITIS

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ALTHOUGH cases of acute hæmorrhagic encephalitis were described as early as 1892 (Leichtenstern, Furbringer, Koenigsdorf) and were undoubtedly seen in the pandemics of influenza in 1890 and 1918, there have been few reports in recent years

Leigh (1946) described 2 cases of encephalitis during the influenza type-B epidemic of that year, Holmes (1947) recorded encephalitic symptoms following atypical pneumonia, and Jennings (1952) reported a case in which a patient with basal pneumonia and a rising type-A antibody titre developed neck stiffness and an abnormal cerebrospinal fluid (C S F)

Of 91 cases of encephalitis notified in England in 1951, 4 were listed as postinfluenzal (Conybeare 1952) Crome (1954) reported 3 adult cases of encephalitis occurring in Slough during the 1951 epidemic of influenza type-A Fernandez (1956) described a fulminating encephalitis in 7 infants, which he thought followed on influenza

During the current epidemic of influenza type-A (" Asian flu ") 2 children with an encephalitic illness were admitted to Queen Mary's Hospital for Children within three days of each other Both attend school in Caterham and had had recent contact with influenza at school and at home The clinical course was so similar that we believe that they had the same disease

Case-histories

Case 1.—A girl, aged 13, was admitted at 8 A M on Oct 17 After being at home with a severe cold for two weeks she had returned to school on Oct 15 Her nose was still blocked and she had a slight cough On the 16th she felt drowsy after coming home from school She was restless and moaned throughout the night At 6 A M she was found to be unrousable and incontinent of urine

On admission she was severely ill, unconscious, and very restless and irritable, with some degree of photophobia There was very little response to painful stimuli Her neck was slightly stiff and Kernig's sign was positive The right pupil was smaller than the left but the light reflexes (direct and consensual) were unimpaired The tone of the limbs was increased, with variable rigidity and athetoid movements of the arms (somewhat reminiscent of cerebral palsy) On the left side the biceps-jerk was absent, the knee-jerk increased, and the plantar response extensor

There were crepitations in both lung fields but no other pneumonic signs Temperature 97°F, pulse-rate 120 per min, respirations 25 per min and regular The C S F was clear and colourless, with 6 lymphocytes per c mm, and protein 50 mg and sugar 75 mg per 100 ml Globulin was not increased, and no organisms were found on staining or subsequent culture Blood-count 9000 white cells per c mm (neutrophils 78%, lymphocytes 17%, monocytes 5%) Blood-sugar and blood-electrolyte levels normal Urine contained acetone

She was given prophylactic penicillin, intravenous dextrose-saline solution, and paraldehyde to control the restlessness

On the evening of admission (Oct 17) her temperature was 102°F and her condition critical There was no change in the level of consciousness Both pupils showed repeated variation in size and in response to light

On Oct 18 she was still in coma but swallowed small quantities of fluid She was still incontinent of urine In addition, hyperventilation and mild tetany developed The C S F was again clear, with 10 lymphocytes per c mm and protein 35 mg and sugar 80 mg per 100 ml Direct smear and culture again negative

On Oct 19 her general condition was better and she seemed to improve for short spells when she would open her eyes and gaze about

On Oct 20 she made a dramatic recovery, spoke rationally, and took fluids and biscuits in the evening, though very sluggish The left leg was still hypertonic, with an extensor plantar response She was continent of urine The temperature was normal

By Oct 24 there were no abnormal signs in the nervous system, and she was allowed up in a chair

When discharged fully ambulant on Nov 2 she had no residual symptoms or abnormal signs

Complement-fixation tests for influenza-A antibodies gave a titre of 1 64 on Oct 21 and the same on Nov 1

Case 2—A boy, aged 10, was admitted on the afternoon of Oct 19 His illness had begun five days previously with a cough lasting two days, anorexia, and general malaise On Oct 17 vague abdominal pain developed, with bouts of vomiting which persisted About five hours before admission he became drowsy

On admission he was severely ill, unconscious, and restless He responded sluggishly to painful stimuli but did not obey commands There was no neck stiffness but Kernig's sign was positive Tendon-jerks were all present and brisk The plantar response was bilaterally extensor Muscle tone was normal Temperature 98°F, pulse-rate 110 per min

The C S F was clear and colourless, with no cells, protein 20 mg per 100 ml, and no increase in globulin No organisms were seen on the stained centrifugate and no growth resulted from subsequent culture

An intravenous infusion of dextrose-saline and Hartmann's solution was given into the right leg and restlessness was controlled with paraldehyde

On Oct 20 his condition was unchanged, though he could swallow small quantities of water His temperature did not exceed 99°F

On Oct 21 he made a dramatic recovery, returning to full consciousness within six hours The plantar response became flexor Lumbar puncture on Oct 22 produced a clear fluid containing no cells, 15 mg protein per 100 ml, and no increase in globulin No organisms were grown Blood-count 12,000 white cells per c mm (71% were neutrophils, 23% lymphocytes, and 6% monocytes)

When allowed up on Oct 25 he was found to have a foot-drop on the right side with gross weakness of the anterior crural and peroneal groups of muscles The distribution of the motor and sensory involvement was in keeping with a lesion of the lateral popliteal nerve There was no other evidence of focal involvement of the nervous system

Complement-fixation tests for influenza-A antibodies gave a titre of 1 4 on Oct 21 and 1 16 on Nov 2

Discussion

These two children had a severe encephalitis after a relatively minor illness Both passed into coma in less than twelve hours with extensor plantar responses and no significant abnormality in the cerebrospinal fluid In case 1 there was evidence of focal signs in the nervous system on the left side of the body, but in case 2 there were no localising signs After being gravely ill in coma (for three days in case 1 and thirty-six hours in case 2) both made a rapid recovery The residual lesion of the lateral popliteal nerve in case 2 is hard to account for except as due to trauma, but there was no direct evidence of trauma to the nerve by splintage or otherwise in the course of the intravenous infusion

The fourfold rise in titre in the complement-fixation test in case 2 indicates infection with influenza virus A The initial high titre in case 1 signifies a recent infection with influenza virus A (Stuart-Harris 1953)

The general course of the illness was very similar to that in children with influenzal pneumonia admitted during the present epidemic—namely, an acute illness lasting two or three days, with a fairly rapid onset and rapid recovery from the acute phase

Neither child has had recent vaccinations or any of the illnesses known to cause encephalitis The evidence favours a diagnosis of acute encephalitis due to influenza virus A rather than sporadic encephalitis happening to coincide with an outbreak of influenza (Stuart-Harris 1953)

I am grateful to Dr David Lawson for permission to report his cases, and to Dr G T Stewart (pathologist to the hospital) and the Public Health Laboratory, Colindale, for the complement-fixation tests

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PERFORATION OF THE COMMON CAROTID ARTERY BY A FOREIGN BODY IN THE PHARYNX

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Massive hæmorrhage due to swallowed foreign bodies is most commonly caused by perforation of the aorta Barrie and Townrow (1946) collected 80 such cases Perforation of a major blood-vessel in the neck appears to be much rarer, and very few cases have been reported in recent years, but Schlemmer (1929) collected 29 cases up to that date, and in 17 of these a common carotid artery was involved

The following case is unusual, and has several interesting features, not the least of which is that the patient recovered, thanks largely to a fortuitous circumstance that made the foreign body easy to remove

Case-report

A married housewife, aged 51, was brought to hospital on Aug 12, 1956, about thirty minutes after a severe hæmorrhage from her throat She was in a collapsed state and her history was obtained partly from her husband and partly from herself when she had recovered somewhat About four weeks previously, while she was eating her dinner, a lump of meat stuck in her throat. She pushed it down with her fingers but felt pain in her throat Fearing that a fragment of bone might have become lodged she went to the casualty department of a local hospital and was reassured Dysphagia persisted but improved over the ensuing few weeks Suddenly, on the evening of admission, just after she had coughed, bright blood began to pour from her mouth, and shortly afterwards she fainted. The bleeding abated after an estimated loss of about two pints, and she was brought to hospital without delay She was admitted to a medical ward because the bleeding was at first thought to be a hæmatemesis or a hæmoptysis

She was pale and shocked, with temperature 97 F, pulse-rate 110, blood-pressure 100 40 mm Hg, and an ill-defined firm swelling deeply placed in the left side of her neck. Physical examination revealed no other abnormality Chest radiography showed normal lung fields

Treatment and Progress—Her general condition improved steadily with anti-shock treatment, including blood-transfusion, but during the ensuing twelve hours she regurgitated small amounts of altered blood at short intervals The swelling in her neck appeared to diminish during this period The amount of hæmoglobin in her blood eight hours after admission, by which time she had received two pints of blood, was only 48% By this time it was clear that the hæmorrhage had come from a lesion in her pharynx or upper œsophagus, and a surgical opinion was sought I first saw the patient fourteen hours after admission, and at this time, though pale, her general condition was satisfactory The only abnormality was an elongated pulsatile swelling some 3 in × 1 in in the position of the upper part of the left common carotid artery

Direct Pharyngoscopy and Œsophagoscopy—Under general anæsthesia the pharynx was first inspected with a long laryngoscope A thread-like structure lying against the posterior wall of the hypopharynx was grasped with forceps and pulled out It proved to be a length of thread, and with it came a somewhat corroded sewing-needle 1¼ in long, which had providentially remained threaded After this there was no further hæmorrhage

Postoperatively penicillin was administered for five days, and the patient made an uneventful recovery The swelling in her neck disappeared within a week

The patient recalled that, about a month previously, she had served a meal after she had been sewing She thought that she must have put her needle into the front of her dress and that it must have dropped into the meat as she bent over to serve it

Discussion

The diagnosis was not so straightforward as might be supposed, partly because the patient was unaware that she had swallowed the needle, and partly because she was too ill after the hæmorrhage to emphasise the amount of dysphagia she had had during the previous month Chest radiography showed no abnormality in her lung fields, but reinspection of the film subsequently showed the needle clearly at the extreme upper end of the radiograph When the wet plates were examined originally this part of the radiograph had been obscured by the frame carrying the film The swelling in the neck was evidently a hæmatoma caused by bleeding into the tissues of the neck at the time of the original hæmorrhage The regurgitation of altered blood during the twelve hours after admission was associated with considerable diminution of the hæmatoma, suggesting that it was discharging into the pharynx

Perforation of a major artery usually follows the swallowing of a foreign body only after an interval of several days In this case the interval was a month Schlemmer (1929) explained this latent period by pointing out that a foreign body would not readily enter a mobile structure such as a large blood-vessel until that structure had become fixed by inflammation in its neighbourhood and, perhaps, softened by the same process Continued pressure would then lead to gradual erosion of the vessel wall

These was no evidence of sepsis in the present case, but it is certainly a factor of importance in some cases, such as that in which a foreign-body perforation of the wall of the right pyriform fossa had caused a parapharyngeal abscess (Thomson and Negus 1949) This had led to sloughing of the wall of the common carotid artery with fatal hæmorrhage It is, however, quite possible for a sharp foreign body rapidly to penetrate the wall of the gullet and of a neighbouring vessel Sneller (1936) described a woman who had sudden pain in the neck while eating chicken and rapidly developed a cervical hæmatoma An impacted bone was seen on endoscopy but could not be removed, because blood obscured the field of vision

Fatal hæmorrhage due to perforation of the œsophagus by foreign bodies is commonly preceded by a smaller warning hæmorrhage If the possibility of a foreign body were considered in every case of bleeding from the pharynx or the œsophagus or of unexplained hæmatemesis, mistakes would be avoided, and timely operation might well save life

Summary

Severe hæmorrhage followed perforation of the common carotid artery by a needle swallowed a month before Removal of the needle was followed by an uneventful recovery

I wish to thank Dr J W Joule, under whose care this patient was admitted, for permission to publish this report

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Preliminary Communication

TECHNIQUE OF HUMAN BONE-MARROW TRANSPLANTS

THE successful transplantation of bone-marrow in mice[1] and rabbits[2] after whole-body X-irradiation has revived hopes that bone-marrow could be satisfactorily transplanted in man[3] The potential danger of whole-body irradiation, which is a hazard for all workers in nuclear irradiation, indicates the need to explore this possibility We have attempted marrow transplantation in five cases and feel that the results may be of interest

The Recipients

Four of the patients had advanced malignant disease and anæmia, with leucopenia or thrombocytopenia indicating grave damage to the marrow, confirmed by marrow examination This precluded further radiotherapy The fifth patient had aplastic anæmia after being successfully treated for carcinoma of the vocal cord a year previously

The Marrow Suspensions

Donor marrow was obtained by multiple puncture of iliac crests of relations who had the same ABO and rhesus blood-groups as the patient and whose red cells were compatible with his serum Four parts of the marrow aspirated were added to one part of sterile acid-citrate dextrose solution, and these suspensions were injected into the recipient as soon as possible after collection

Administration

In three cases the suspension was introduced into the descending aorta, by catheterising the femoral artery (two cases) or the left radial artery (one case) In the fourth case it was introduced by percutaneous puncture of the abdominal aorta In the fifth the suspension was injected intravenously The reason for choosing the aortic route in cases 1, 3, 4, and 5 was that the pelvis and lumbar vertebræ had been deliberately irradiated in the previous fortnight to destroy the cells present and produce hyperæmia, thus providing a suitable site for the injected marrow

The amounts of marrow obtained and injected were

Case no	Age (yr)	Sex	Weight (kg)	No of donors	Volume injected (ml)	No of cells injected	No of cells per g body-weight (× 10⁴)
1	25	F	50	3	43	$1\,019 \times 10^{9}$	2 04
2	11	M	50	1	25	$0\,575 \times 10^{9}$	0 115
3	14	F	30	3	44	$1\,188 \times 10^{9}$	3 96
4	66	F	46	4	47	$1\,06 \times 10^{9}$	2 30
5	67	M	63	3	48	$0\,897 \times 10^{9}$	1 42

All the patients received prednisone 30 mg daily both before and after the infusion of marrow

Results

Case 1—A woman, aged 25, with advanced Hodgkin's disease On Nov 5, 1956, 43 ml of suspension was injected from a catheter into the aorta at the level of the 8th dorsal vertebral body This produced no symptoms No improvement followed No evidence of the injected cells was found at necropsy 3 days later

Case 2—A boy, aged 11, with aplastic acute leukæmia and staphylococcal septicæmia On Dec 14, 1956, 25 ml was injected intravenously No untoward symptoms No improvement noted At necropsy 10 days later there was no conclusive evidence of injected marrow

Case 3—A girl, aged 14, with neuroblastoma with multiple deposits in skeleton and soft-tissues On June 19, 1957, 44 ml of suspension was injected by percutaneous aortic puncture Patient died from retroperitoneal hæmorrhage after completion of this operation

Case 4—A woman, aged 66, with advanced lymphatic leukæmia had her pelvis irradiated to a skin dose of 2500r Puncture of an iliac crest immediately before infusion showed no nucleated red blood-cells On Aug 13, 1957, 47 ml of suspension was injected by catheterisation of a femoral artery at the level of L2 The patient tolerated this well and showed considerable clinical improvement A month later nucleated red cells were readily seen in the iliac-crest marrow obtained by puncture This patient is still alive, and the procedure appeared to improve her general condition very greatly This patient is still alive (Jan 9, 1958) and is in fair general health Her leukæmic condition is unchanged

Case 5—A man, aged 67, with aplastic anæmia had been successfully irradiated for carcinoma of the larynx His pelvis and upper femora were irradiated to a dose of 2800r (skin dose) This was followed by 15 mg of nitrogen mustard ('HN2') as a single injection 48 hours before the infusion of marrow This was to depress further the reticuloendothelial system On Oct 10, 1957, 48 ml of suspension was injected by catheterisation of a femoral artery This man feels better for the procedure The white-cell count, which previously was 500 per c mm, is now 1000–1500 per c mm A comparison of sternal and iliac marrow taken at the same time a month later shows more nucleated red cells (18 8%) in the iliac-crest specimen than in the sternum (9 2%) This patient died of bronchopneumonia on Dec 9, 1957

These results show that it is technically possible to inject marrow cells in man It would be desirable to increase the amount injected In this connection the use of marrow from ribs surgically excised for non-malignant conditions is being explored In the two examples we have studied, suspensions containing more than $1\,5 \times 10^{9}$ cells were readily obtained from each rib

In conclusion we wish to emphasise that this is purely preliminary work

We are grateful to Sir Stanford Cade Mr E Stanley Lee, and Dr C J Gavey for permission and encouragement to treat their cases, and to Dr B Strickland, of the radiodiagnostic department, for his invaluable assistance

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Growth of Viruses

AT a meeting of the section of pathology on Dec 11, Prof H B MAITLAND said that the mechanism of reproduction of bacteriophage had been taken as a prototype of virus reproduction in general The desoxyribonucleic acid (D N A) of the phage alone entered the bacterial cell and determined the synthesis of phage D N A and protein, which were organised at a later stage into morphologically mature phage particles These particles were released by bursting of the bacterium During the earlier part of the process of reproduction no infective phage was found in the cell, and this period had been referred to as an "eclipse phase"

The ribonucleic acid (R N A) of tobacco-mosaic-disease virus played a similar role in the reproduction of this virus (T M V) It determined the infective property of the virus and the nature of the lesions produced The R N A of one strain had been combined in vitro with the protein of another to make a hybrid strain of T M V virus Plants infected with such hybrid strains had symptoms characteristic of the strain, providing the R N.A and the new virus produced as a result of infection corresponded in every respect with the R N.A -donor strain, R N A could be extracted from T M V -diseased plant material and was itself infective, causing characteristic symptoms and the production of new complete virus

An alternative method of reproduction was by binary fission, as in bacteria and in certain rickettsiæ The reproduction of animal viruses might be by binary fission, or it might be similar to bacteriophage with an eclipse phase as part of the process, but some intermediate form of reproduction might exist

The psittacosis virus and other closely related viruses multiplied by developing large forms which increased in number by binary fission and later subdivided into the smaller bodies which were the naturally infective virus Because of their method of division psittacosis and similar viruses were regarded as resembling the rickettsiæ rather than the viruses

The vaccinia virus representing the "pox" group of viruses was next to the psittacosis group, and morphological studies of ultra-thin sections of infected tissue had not suggested reproduction by binary fission Growth curves of vaccinia in the chorioallantoic membrane of the developing chick embryo, as well as in a number of systems of tissue and cells incubated in nutrient media in vitro, had been studied, but further work was required to elucidate the mechanism of growth of vaccinia virus

Nucleic acid, which was itself capable of transferring infection to susceptible animals, could apparently be separated from tissue infected with meningoencephalitis virus and with eastern equine encephalomyelitis virus, and this seemed to bring these two animal viruses into line with bacteriophage and tobacco mosaic virus with regard to the role of nucleic acid in virus reproduction

Reviews of Books

Rheumatoid Arthritis

CHARLES L SHORT, M.D, WALTER BAUER, M.D, WILLIAM E REYNOLDS, M.D Cambridge, Massachusetts Harvard University Press London Oxford University Press 1957 Pp 480 55s

THIS book is based on a study of 293 patients with rheumatoid arthritis at the Massachusetts General Hospital, who have been followed for at least twenty years Findings were recorded on a predetermined plan and according to presenting symptoms and signs (which are compared with those of a non-rheumatoid control series) The patients' subsequent histories are analysed in great detail

Tracing the evolution of the concept of rheumatoid arthritis, Dr Short and his colleagues show that most previous students of arthritis have failed to distinguish degenerative from rheumatoid joint disease in published series of patients The authors set out their own criteria for diagnosis, and while they have undoubtedly avoided previous pitfalls, it is a weakness of their otherwise excellent analysis that they have included under the heading of rheumatoid arthritis 44 patients with spondylitis, as well as 10 with psoriasis and arthritis and 3 with ulcerative colitis and arthritis Most opinions (supported by the recent evidence of the specific agglutination tests for rheumatoid arthritis) would nowadays distinguish these conditions as separate diseases Nevertheless this book is one of the most authoritative and comprehensive studies of rheumatoid arthritis yet published It is in the highest tradition of medical scholarship and will remain a standard work of reference for many years

Deafness, Mutism and Mental Deficiency in Children

LOUIS MINSKI, M.D, F R C P, D P.M, consultant psychiatrist, Royal National Throat, Nose and Ear Hospital, London. London Heinemann Medical Books 1957 Pp 82 12s 6d

THE difficulty of distinguishing between deafness and mental deficiency has only lately been appreciated Many children whose disturbed behaviour had been attributed to mental deficiency have been discovered to be deaf and within the normal range of intelligence The child who is both partially deaf and mentally retarded is particularly hard to assess For the past five years Dr Minski has been able to study such problems in the research unit for children at Belmont Hospital, and this small book summarises his experience and opinions

He discusses the general aspects of the subject and gives the relevant clinical data, before describing the layout and staffing of the Belmont unit and the methods of assessment Short notes follow on audiometry, electrophysiological methods of assessment and psychological testing by the Dreyer-Collins and Merrill-Palmer tests Although Dr Minski is to be congratulated on drawing attention to the problem of the deaf who have been erroneously diagnosed as defective, he has by implication been of less service to the mental defective who is not deaf Unfortunately in the first sentence of the first chapter he quotes the definition of the "feebleminded" child from the original Mental Deficiency Act of 1913, without reference to the amendments effected by the Education Act of 1944 relating to the "educationally subnormal" child It is also disappointing to those who are trying to improve the training of mentally defective children for a note on the dust cover to refer to such children as those "for whom nothing can be done"

It is to be hoped that Dr Minski will, in a second edition, amplify his theme by a more detailed exposition of clinical matters relating to deafness and also put into better perspective the problem of the mentally defective child, especially since the publisher has abbreviated the title on the cover to Mental Deficiency in Children

An Introduction to Functional Anatomy

DAVID SINCLAIR, M.D, professor of anatomy, University of Western Australia Oxford Blackwell Scientific Publications 1957 Pp 426 42s

WHILE teaching at Oxford, Professor Sinclair lectured for some years at the Dorset House School of Occupational Therapy, and his new text is closely linked to the syllabus for occupational therapists, and for those with similar needs, such as physiotherapists As is customary in such circumstances, anatomy and physiology are combined

Like all who attempt simultaneous description of structure and function, Professor Sinclair meets difficulties But though his book may appear at first sight to be divided into a first part largely dealing with function, and a final section actually entitled Topographic Anatomy, careful reading will show that in fact *anatomy and physiology* are far more closely interwoven than is apparent from the table of contents

This bold attempt is on the whole successful It is a pity though that the integration of the autonomic with the rest of the nervous system is not brought out more clearly Some readers may wonder too whether the orthodox insistence on a primary protective function in the ribs is not medical rather than biological The distinction is not made between primary cartilaginous joints and sutures, as growth mechanisms, and the true locomotor joints of the body These are small criticisms, but in a book which in title puts the accent on function, such matters should be given more clarity than is usual in strictly anatomical texts

The book ends with an excellent glossary and even a small bibliography Illustrations are simple but adequate In all it is a most readable work, which deserves and can be recommended to a far wider circle of readers than the one to which it was immediately directed.

Suburban Neurosis Up to Date

It is now nearly twenty years since Taylor[1] described in our columns a condition which he called "suburban neurosis" He was writing about life in the new housing estates which had sprung up round our great cities In these estates—sometimes jerry-built and almost always devoid of social amenities—it was considered correct to keep oneself to oneself The one-child family and the baby car represented the height of ambition, and, though physical health was comparatively good, many of the people had anxiety states, often with hysterical features and reactive depression, which Taylor attributed to boredom, loneliness, and a false set of values One of the happier results of the 1939–45 war, and particularly the continuing threat of air-raids, was to build a new community life in such places Fire-watching, the Women's Voluntary Services, evacuation, and many forms of mutual help broke down the previous social isolation, and the prevalence of neurotic illness declined spectacularly Afterwards there was some slipping back, but the social isolation of the inter-war years has not been fully restored

Since the war, the emphasis of building development has changed Green belts of a sort have been established around the cities, and instead of the speculative hire-purchase estates we have had huge blocks of municipal flats, large out-county municipal estates, and the new towns (Only within the past three years has speculative building recommenced, and its scale is much smaller than before) Though redevelopment in municipal flats has had its social difficulties, old ties of friendship and kinship have not been broken, as must happen when a family moves right out of the city In the new towns, industry and homes have moved out together, and imaginative social provision has done much to reduce the risk of neurotic reactions in a new environment—though the combination of high rents, hire-purchase payments for furniture, and rapidly increasing families often leads to justifiable financial anxiety[2] The out-county municipal estates, however, have long been suspected of partly repeating the story of the pre-war speculative estates Great working-class populations were translated to new homes in country suburbs, and, though the standards of housing were admirable, social provision was at first very meagre the great majority of the wage-earners continued to earn their living in London, while the women tended to follow the obsolescent middle-class pattern of social isolation as a standard of respectability Hence it was good that a team from what was then Prof J M Mackintosh's department at the London School of Hygiene should decide to make a detailed study of what was going on in one of these out-county estates to the north of London Two reports of this team's work appeared last year,[3] [4] and a third, by Martin, Brotherston, and Chave,[5] deals with the incidence of neurotic and psychotic illness

Four sources of information were tapped—mental-hospital admissions, referrals to psychiatric outpatient clinics, general-practitioner consultations, and the results of a direct-interview survey Between 1949 and 1954, there were 129 admissions to mental hospitals from the estate, giving a rate slightly more than 50% above what would be expected from national figures Admissions for neuroses were twice the national rate, with neurotic reactive depression among females predominating On the other hand, the discharge-rate was high, and the average period in hospital short Psychiatric outpatient referrals did not differ markedly from the national average, but were twice as numerous as in neighbouring areas served by the same hospitals During 1953, all the doctors in general practice on the estate maintained records of all their consultations, and the following table shows the number of patients consulting them for various complaints (per 1000 registered population) set alongside "expected" figures

Diagnosis	*Actual estate figure*	*Expected estate figure on national basis*
Psychosis	3 0	1 0
Anxiety neurosis	23 4	11 8
Disturbances of sleep	25 6	6 3
Anorexia	9 7	2 1
Palpitations	1 1	0 2
Debility and undue fatigue	50 9	13 3
"Depressed" or depression	7 0	3 3
Headache	29 6	10 0
Urticaria and allergic rash	24 8	19 5
Duodenal ulcer	10 2	3 9
Asthma	12 1	7 6

The direct-interview survey showed that the self-estimate of "nerves" on the estate was 223 per 1000 adults, compared with the national figure of 126 obtained by the Social Survey of Sickness[6] Complaints of neurotic symptoms were higher among those who had lived on the estate for two years or less than among those who had been there for three to six years, but even the oldest inhabitants had rates far above the national figures Admittedly, rehousing on an out-county estate is partly determined by medical certificate, but a psychiatric or quasipsychiatric diagnosis had been submitted for only 2% of men and 8% of women, and these can account for only a small part of the excess of neurotic illness encountered

Here, then, is the suburban neurosis presenting itself again, and probably for much the same reasons As Professor Brotherston and his colleagues remark, each family "keeping itself to itself" generates a degree of loneliness and social isolation inconsistent with good mental health The findings at direct interview and the statistics for juvenile delinquency suggest that, with time, there is a slow improvement, but the picture remains a sad one Physical planning on the out-county estates appears to be out of step with social planning, and rehousing has improved physical environment at the cost of mental wellbeing There is reason to think that in the new towns the lessons of the past have been learnt and applied Precise statistical evidence has yet to be collected, but we agree that "comparable studies of mental health problems in New Towns would be especially illuminating" The present study supports the view that social environment affects the prevalence not only of neurotic but also of psychotic illness, and, if this is so, the future of preventive psychiatry will lie as much in social planning as in early diagnosis and treatment A few thousands of pounds spent on social amenities and social development may save hundreds of thousands used on therapeutic services or wasted in labour lost

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Artificial Insemination

ARTIFICIAL insemination of livestock is now widely practised, and its techniques are both simple and reliable There are few practical difficulties in carrying out the same process in human beings, and most of what has been written on this subject turns on the desirability of doing so In a new review[1] of the human applications of the method, a Dutch obstetrician and gynæcologist deals with both types of insemination now in use—from the husband and from a donor or donors He discusses techniques, but he is more closely concerned with far more contentious matters Few biological discoveries trespass on so many sensitive areas of human belief, and the body of resulting comment—legal, religious, and ethical—is the main topic of Dr SCHELLEN's review For some commentators every stage of the process, from the manner of collecting semen and the desirability of paying the donor to the risk of inadvertent marriage between siblings, is of immediate and serious moral importance Others are more preoccupied with the effects on parents, child, and doctor of granting or refusing a request for donor insemination In the discussion of these possible effects, rationalisation often plays a recognisable part SCHELLEN does not wholly escape the charge of special pleading in his chairmanship of the debate, and his *parti pris*, although evident, is overtly declared only in his last few pages But his book is a fascinating study of the social anthropology of human opinion

Such an alarming battery of theological, moral, magical, psychological, and admonitory comment is likely, thus presented, to deter any cautious doctor from involving himself, at least in donor insemination, and the deterrent action was perhaps SCHELLEN's aim Many whose ethics are based on similar religious belief may well agree with his assessment and emphasis To others, it may seem that patients seeking medical help in their desire for children are less agitated by scruple over details of procedure than are their spiritual mentors At the same time, the possibility of all kinds of trouble arising from donor insemination must be evident to all but the blindly sanguine SCHELLEN quotes many such forebodings, the actual failures he mentions are largely anecdotal But his book poses once more one of the central questions of medical ethics—how the moral and religious opinions of the doctor and his patient should determine the advice given in matters of conduct He offers only conjecture on the motives which lead patients to request donor insemination These are important and probably diverse it would be possible to take the extreme position that well-adjusted patients will not require donor insemination, and the ill-adjusted may be harmed by it, such a view leads, at least, to dignified inactivity Some doctors believe that donor insemination has a valid place in medical practice, and meets both a demand and a right There are those who would no doubt agree with GUTTMACHER,[2] both in his summary handling of the theologians and in his general advice—that the doctor should act on his judgment and knowledge of the patient, with privacy and without formality of any kind, avoiding the formidable legal instruments prepared by some authorities bent on self-protection, refusing high fees, and "putting the name of the husband as father on the appropriate forms—a white lie here is a humane, friendly deed" At the opposite extreme, there is anxious debate whether a donor who accepts payment is morally fit for fatherhood, or whether he is entitled to demand it for "a service more distasteful than that of a blood donor" Even the use of the husband's semen gives rise to heart-searching in some places Every approach, from an ingenuity of scruple worthy of *Hudibras* to frank commercialism, is cited in SCHELLEN's collection the only criticism of its scope is that this citation of extremes leads to an under-representation of more moderate judgments

Since many critics of artificial insemination base their objection, at least in part, on genetic and psychological risks, it is unfortunate that we have here no follow-up studies of couples who have borne a child in this way, and no serious discussion of the biological implications in terms of modern genetics Evidence of this kind might form a more manageable basis for advice than appeals to general, or even infallible, moralities The genetic comment is uncritical, both in exaggerating by implication the physical consequences of accidental endogamy, and in accepting anecdote—about supposed man-ape hybridisation, for example There are those who will read Dr SCHELLEN with irritation, but the human anxieties he writes of are real and deepseated, even when unspoken Mountains of this kind have to be scaled by the patient, even when they have been made from what, to the unconvinced sceptic, appear to be ethical molehills Some of the instances of medical insensitivity to which SCHELLEN refers are warnings against overconfidence and undue persuasion

Eradication of Malaria

MALARIA eradication, though known to be feasible, might have been pursued only exceptionally but for the fear that, owing to the growth of anopheline resistance, control by means of residual insecticides could not be maintained permanently The W H O Expert Committee on Malaria, in recommending eradication,[3] points to its social and economic advantages, and remarks that it needs special finance for a limited time only Moreover, in achieving eradication a government gains an asset in well-trained staff available for other services

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[1] Artificial Insemination in the Human By A. M C. H SCHELLEN, M D, resident at the department of obstetrics and gynaecology, University Hospital Groningen New York Elsevier London Cleaver-Hume 1957 Pp 420 72s

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Annotations

INFLUENCE OF ACID-BASE BALANCE ON THE ACTION OF DRUGS

CHANGES in acid-base balance have long been known to influence both the therapeutic and toxic effects of salicylates Administration of sodium bicarbonate reduces the toxicity and plasma level of salicylate[1], and Smith et al[2] showed that this was due to increased rate of excretion of salicylate in alkaline urine The clearance of unconjugated salicylate is much lower than that of inulin in acid urine, but is higher in alkaline urine[3] Hyperventilation and acetazolamide, both of which produce an alkaline urine, are as effective as sodium bicarbonate in increasing salicylate excretion[4] Since acetazolamide produces systemic acidosis,[5] the increased salicylate excretion in alkaline urine must be directly related to the urinary pH and not to change in systemic acid-base balance

More recently the excretion of two other important drugs, phenobarbitone and mecamylamine ('Inversine'), has been shown to resemble that of salicylate Phenobarbitone, which is a weak acid, is excreted more rapidly when the urine is alkaline[6] Barbitone itself, although also largely eliminated in the urine, is little affected by variation in acid-base balance Mecamylamine, a weak base, is excreted more rapidly when the urine is acid[7–9] Other ganglion-blocking drugs, such as hexamethonium and pentolinium, are much stronger bases and are unaffected by acidosis or alkalosis Many other weak bases, including mepacrine and chloroquine,[10] [11] procaine,[12] and quinine,[11] [13] are excreted in the same way as mecamylamine Variation in excretion-rate in the case of the weak-base drugs is, however, of little importance since only a small proportion of any dose appears in the urine Alkalinisation of the urine increases the hypotensive effect of mecamylamine,[8] [9] and reduces the toxicity of phenobarbitone and salicylate Acidification of the urine by ingestion of ammonium chloride has the opposite effect Treatment with sodium bicarbonate has been recommended both in salicylate[4] and in phenobarbitone[6] poisoning Other workers have recommended dialysis with the artificial kidney in salicylate[14] and barbiturate[15] intoxication Probably the ideal method of removing the drugs from the body in severe poisoning is a combination of the two methods

Variation in the rate of excretion of these drugs influences the amount retained in the body, and therefore there is a gradual modification of their pharmacological effects In contrast, sudden changes in systemic acid-base balance may rapidly alter the distribution of drugs within the body, while the total amount remains unchanged This may be associated with corresponding change in their specific action Respiratory acidosis induced by breathing 10% CO_2 increases the plasma levels of the bases mepacrine and chloroquine[16] and of mecamylamine,[17] but reduces those of the acids phenobarbitone[6] and thiopentone[18] Except in the case of thiopentone, this is associated with a reverse change in the intracellular concentration of the drugs Thiopentone is largely stored in adipose tissue, and in this case acidosis causes mobilisation of the drug from body fat[18] An increased plasma level caused by acid-base change increases the pharmacological effect of mecamylamine,[17] but reduces that of phenobarbitone[6] This observation may be of considerable practical importance during anæsthesia

VIRAL HEPATITIS

VIRAL hepatitis remains common, and, though mortality rarely exceeds 0 2–0 5%, the illness may be long and unpleasant and permanent hepatic damage the final result Large epidemics are fortunately rare, but under conditions of war or civilian catastrophe big outbreaks have been common during the past two centuries The disease has been intensely studied in recent years, and it was the subject of a symposium at the last annual meeting of the American Medical Association Advances in treatment have unfortunately been trivial, but some progress in the understanding of ætiology and epidemiology has been achieved and was well reviewed at the symposium by Havens[19]

The two varieties of the disease are distinguished mainly by the route of infection and the incubation period The causal agent of the naturally acquired disease (infective hepatitis) can be demonstrated during the period of infectivity in the blood-stream as well as in nasopharyngeal washings and in the fæces The second variety of the disease has been given the name "homologous-serum jaundice" and the causal agent has been found only in the blood of patients and never in the pharynx or fæces This second variety is transmitted only as a result of artificial procedures—e g , blood-transfusions or injections given with an imperfectly sterilised syringe Transmission of infective hepatitis, on the other hand, is usually by close personal contact or by fæcal contamination of food or water, but, since the virus is also present in the blood-stream at least for some days or weeks, it can also be transmitted in the same way as homologous-serum jaundice

The viruses responsible for these two diseases belong to the class of filter-passers, and they are both remarkably resistant to chemical and physical methods of sterilisation The relationship between them remains an intriguing problem The coincidence between outbreaks of hepatitis among patients attending venereal-disease clinics for arsenical therapy and the presence of an epidemic of infective hepatitis in the same locality suggested a close connection between the viruses[20] But the fairly consistent and striking difference between the incubation periods of the two forms of the disease and the difference in the distribution of viruses in the infected person rules out the possibility that the viruses are identical This conclusion is firmly supported, moreover, by two further pieces of evidence Firstly, the agent of infective hepatitis confers a strong and lasting immunity against reinfection by infective hepatitis, without apparently enhancing the resistance to the serum jaundice Secondly, an injection of normal adult human gamma-globulin gives considerable protection against infective hepatitis but is without demonstrable effect against the other form of the disease Nor can these differences be entirely attributable to the different routes of infection, since parenteral transmission of infective hepatitis results in a disease with the characteristic short incubation period and the appearance of the virus in the throat and fæces The conclusion, therefore, that virus hepatitis may result from infection by either of two immunologically distinct agents seems well founded Their usual mode of transmission is equally distinct and well established, and the prophylactic measures are plain All that is required, therefore, to reduce the incidence of this disease is their widespread and meticulous application As Dr Morton remarks in a letter on p 164, efficient syringe sterilisation and a scrupulous injection technique are more than ever important at present, when large programmes of prophylactic inoculation are about to be carried out

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FAILURE TO GAIN WEIGHT IN INFANCY

IN a recent symposium on the relationship between pædiatric disorders and nutrition, Holt[1] discusses excessive loss of nitrogen from the body as a cause of failure to thrive in infancy Cystic fibrosis of the pancreas is one condition in which there is abnormal fæcal loss of nitrogen, and in malignant malnutrition, or kwashiorkor, this fæcal loss is augmented by losses through the kidney It seems likely that in kwashiorkor both digestive and tissue enzymes are deficient, so that much of what little nitrogen is absorbed cannot be used and escapes in the urine Holt also draws attention to the need for caution in the treatment of patients with protein starvation High levels of non-protein nitrogen have been found in the blood of patients with kwashiorkor who were taking protein by mouth,[2] and toxic effects have followed intravenous feeding with hydrolysed protein or amino-acids

Careful investigation of most cases of "marasmus" will often reveal some obvious cause such as a congenital abnormality of the alimentary tract, heart, or nervous system, or perhaps an unsuspected infection On the other hand, much elaborate effort may be needed to uncover certain metabolic anomalies The symposium gives up-to-date information about such disorders as infantile renal acidosis, idiopathic hypercalcæmia, and galactosæmia, and refers to the various types of aminoaciduria In these and allied disorders, the metabolic anomaly may exert its effect largely through impairment of appetite, and calorie losses in the excreta are unlikely to be large unless there is an accompanying glycosuria

Holt also refers to a further group of children in whom there is a discrepancy between the amount of food the child is thought to be taking and the amount he actually receives The difference may be the result of inaccurate or careless preparation of feeds, rumination or unreported vomiting, or, on occasion, downright deceit Such children are often said to be suffering from "mismanagement" or "psychological upset", and a spell under close observation in nursery or hospital may disclose a steady weight gain even though the food intake is apparently no different from that given at home

PRESSURE GROUPS

TODAY the words "pressure group" often drop off the journalist's pen or the orator's tongue, and to most readers and listeners they suggest yet another disagreeable development of the modern world But this reaction is often unreasonable, for it is the name rather than the device that is novel Runnymede, for instance, was the scene of one effective pressure group, and such reforms as the abolition of slavery, the Factory Acts, and (in more modern times) equal pay for women were all initiated by small groups of people, who, by exerting pressure, gradually brought the Government and the public round to their way of thinking Nevertheless, though they can thus claim respectable ancestry and good service in the past, pressure groups, like other useful institutions, are changing with the changing times, and their new name is perhaps a sign of the community's uneasy recognition of their growing importance and power The part they are now playing in the political life of the nation is examined with discernment and tolerance in the current issue of the *Political Quarterly*,[1] where the social scientist as well as the politician will find much of interest

As the machinery of government has changed, so have the methods of the pressure group The Runnymede group was small, and its methods direct and swift, but in a parliamentary democracy they would be less effective New means of communication and ease of transport have given the modern pressure group new opportunities, but literacy and universal suffrage mean that it must convince more people if the climate of opinion is to be altered The multiplication of pressure groups has in part been fostered by the Government's pervasion of the life of the citizen To the courts of justice, the Army, and the Navy, for which the State has long been responsible, have been added such diverse enterprises as schools, roads, hospitals, pensions, mines, postal services, and museums, and each addition has provided a focus (or indeed foci) for several pressure groups The Association of the ex-Bowmen of Agincourt, for instance, may have met annually on St Crispin's day, but, unlike the ex-Service associations of our own time, it probably did not press the pension claims of its members

Among these new groups the most conspicuous are the innumerable vocational ones formed by workers, whether members of a profession, traders, or artisans, and Sir Winston Churchill, with his historian's outlook, has perceptively described the trade unions as "an estate of the realm" While some of these are profoundly concerned with the public interest, others are concerned mainly or entirely with the interest of their members

Besides these, however, there are still the groups whose sole purpose is to work for a cause—the legalisation of abortion or the abolition of capital punishment, to take two topical examples True to their traditional pattern, most of these groups are small, with meagre funds, but their influence cannot be measured by their size or their finances, and it is largely through the kind of enlightened and disinterested pressure they exercise that so many wrongs have been righted by persuasion and that British history records so few revolutions Unfortunately today the small ill-financed pressure group may be somewhat at a disadvantage, for publicity has become a more expensive commodity to reach the public's ear and eye usually costs money, while competition for the public's mind and interest is keen It is indeed perhaps a sign of this competition that the Government are themselves beginning to use some of these groups as a means of exerting pressure on the public The subsidies which they offer to bodies such as the Marriage Guidance Council and the National Association for Mental Health are too modest to sap independence, but here is a development which may well initiate yet another morphological type of pressure group

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In many ways the growth of pressure groups, in number and influence, is a healthy sign the device is one which can be used, with typical British economy, either as a spur or a bridle for the Government of the day But with the shifting emphasis of these groups, their growing power, and the preoccupation of so many of them with the rights of limited sections of the community rather than the propagation of ideas and principles, it is essential that the rights of those who are prevented from forming groups, whether by isolation, ill health, youth, or age, shall not be neglected The best of our pressure groups have always been created for the protection of the weak, and, despite all the changes time brings, their true strength will probably always lie in their readiness to recognise where help is most needed

ATOMS, BRONCHITIS, AND CLEAN AIR

THE Windscale accident drew public attention to the risks of the civil use of nuclear power, but these risks are at least foreseen, as the report of the Fleck Committee (summarised on p 157) illustrates To quote the medical officer of health for Wigan,[1] " if the approach to the first industrial revolution had been as carefully and painstakingly controlled as regards the possibilities of environmental hazards to mankind as is the approaching Atomic Age we should now be a much healthier nation "

Nuclear power may in due course help to remedy some defects by freeing us from the need to burn coal in great quantity and so lessening the damage, to ourselves and our buildings, that comes from air pollution We may hope that, before very long, smoky grimy industrial towns, and their coughing citizens, will be as distant memories as the London cholera epidemics are now

Some measure of the havoc caused by the wastes poured into the atmosphere in industrial towns is given in a recent review of bronchitis in Salford [2] In the years 1946–55 the death-rate from bronchitis per 100,000 population in England and Wales ranged from 55 to 84, in Salford the range was 114 to 178 (The death-rates from pneumonia, pulmonary tuberculosis, and lung cancer were all higher in that smoky city than in England and Wales, though the differences were less striking) This implies that the death-rates from bronchitis are very high in Salford—not that they are low in England and Wales in fact they are about 3 times those of Belgium, 6 times those of Germany, 15 times those of France and Scandinavia, and 36 times those of the United States Chronic bronchitis may well now assume the mantle of the vanishing rickets and be called " the English disease " " Men in England awaking and clearing their bronchi before setting out to work make a fearful noise"[3], and in 1956, bronchitis accounted for 5 6% of all the deaths in England and Wales (11 9% in Salford) Moreover, it is the cause of about a tenth of all the days lost from work through illness, and it cost the National Insurance Fund £$7\frac{3}{4}$ million in one year

Admittedly no certain link has been established between air pollution and bronchitis or other respiratory disease, but the epidemiological evidence is very strong [4–7] Smoking aggravates bronchitis, and fog, temperature inversion, and influenza precipitate a rise in the number of deaths (the relationship with influenza epidemics may partly account for the tendency of the death-rate from bronchitis to rise and fall in alternate years) Clean air may come, one day, as a by-product, when nuclear fusion provides most of our power, but many years may slither away before then To use the prospect as an excuse for inaction will cost very many lives and much misery We may wish that our ancestors had not left us with such a legacy of inefficient smoke-emitting devices, but, to quote Dr Hilditch [1] again, " we must make the best of the situation as it exists and improve our environment whenever and wherever we can "

The Clean Air Act lays on local authorities much responsibility for making these improvements, and we hope they will do more than they have yet done [8] to make use of their splendid opportunities of improving our health The fact [2] that the bronchitis death-rate in Japan fell from 44 8 per 100,000 in 1947 to 9 9 in 1955 is both an example of what can be achieved and a stimulus to inquiry as to how it was done

NINETY

IN deciding when to publish an article, we seldom make any serious effort to ensure that it shall appear on the author's birthday But we felt that an agreeable adventitious flavour would be given to Sir Leonard Rogers' latest contribution if we kept it for this week For he was born on Jan 18, 1868

We must wait another ten years before asking Sir Leonard the routine question about the reason for his exceptional longevity, but the explanation certainly cannot be an inactive life His astonishing output of original work comes of a combination of native wit with intense labour His strenuous application to the matter in hand, from his earliest days in medicine, seems to have preserved, instead of impairing, a youthfulness of mind which still enables him to rely on his remarkable memory for detail when he speaks, without notes, on medical subjects Regarding him as a contemporary, we may find it hard to remember that this is the man who introduced emetine for amœbiasis, antimony for kala-azar, and chaulmoogra preparations for leprosy, and who revolutionised the treatment of cholera before he turned his mind to the forecasting and prevention of this devastating disease, on which he is again making important practical proposals Because he is so keen, he has a persuasive habit which gained from many sources large funds for the Calcutta School of Tropical Medicine and later for BELRA—the British Empire Leprosy Relief Association His work has been his passion, and his conversation, as eager and rapid as ever, is of his work, his ideas, and his sons He speaks as he is, a leader of thought and action, but he is never pompous, and his humour remains He has enjoyed his life, as his autobiography *Happy Toil* makes very clear, and we wish him many more years in which he can use his genius to stimulate his juniors

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Special Articles

FORECASTING AND CONTROL OF CHOLERA EPIDEMICS IN SOUTH-EAST ASIA AND CHINA

Sir Leonard Rogers
K.C.S.I., C.I.E., M.D. Lond., LL.D. Glasg., F.R.C.P., F.R.S.
FORMERLY MAJOR-GENERAL, INDIAN MEDICAL SERVICE

In a recent paper (1957) I recorded a tenfold reduction in the cholera mortality during the decade 1946–55 in the extensive endemic area of Lower Bengal—the home of cholera—together with a forty fold to fifty fold reduction in the more extensive epidemic areas of India, including the practical elimination of the disease in the Punjab and North-West Frontier provinces

This unprecedentedly rapid decline in cholera mortality coincided with the general adoption of my suggestion of 1926 and 1928 to inoculate compulsorily the 20 million or so pilgrims, whom I had shown to have played a predominant part in disseminating cholera every year in epidemics over India, and in exceptionally bad years as pandemics over Asia and Europe, &c., during the 19th century

During the fifteen years 1941–55, about 300 million people were inoculated against the disease in India, but during the first five of these years the second world war led to shortage of food and famine conditions, which are always accompanied by a greatly increased cholera incidence, due to widespread movements of the people in search of food These circumstances prevented the full effects of the new plan of control being obtained during 1941–45 The continued use of the new measures during the decade 1946–55 doubtless had a cumulative effect It should be noted that they have still to be tested after widespread failure of the monsoon rains, with inevitable increased cholera incidence (Rogers 1928, pp 27–40) It is, however, a hopeful sign that after a failure of the north-east monsoon rains in the last quarter of 1936, the increase of cholera in South-East Madras was a comparatively mild one

The success of control measures in India led me to extend my epidemiological inquiries to the incidence of cholera during the first half of the present century in South-East Asia and China, in the hope of extending preventive measures over these areas

It was first necessary to establish the areas where the disease is endemic at all seasons of the year because the monthly absolute humidity (i e, the mean water-vapour pressure) does not fall below the critical minimal point of 0 400 in Hg during the winter months, as I showed to be the case in India (Rogers 1926, 1928)

The table shows that in Burma, Thailand (Siam), and Indo-China the lowest early absolute humidities of January and February remain above 0 400, so these are endemic areas Burma is continuous with the endemic areas of Assam and the eastern provinces of Greater Bengal, from which cholera epidemics spread yearly over North-West and Central India, coincidently with the spring rise of the monthly absolute humidity to well above 0 400 The combined endemic areas of Bengal and South-East Asia, as defined above, are indicated by the hatching in the map (fig 1)

On the other hand, China is a huge epidemic area in which the winter absolute humidities fall well below the critical line of 0 400 from November to March from the Yangtse valley northward, as shown by the monthly data of Shanghai near the mouth of the Yangtse river The readings for the southernmost part of China, as illustrated by those at Hong Kong (in December, January, and February 0 405, 0 390, and 0 387 respectively) are on the borderland of the critical point Southernmost China thus corresponds to the eastern sub-Himalayan North-West province of India (Rogers 1928 map VIII, p 222) in being a borderland area where cholera is reduced to very small proportions during the winter, but recrudesces in March with the rise of the absolute humidity to over 0 400 Later the cholera spread farther to the north-west with the rise of the absolute humidity to well over 0 400 just as it does over Central and Northern China in epidemic years

It was therefore necessary to study the annual incidence of cholera in South-East Asia, its possible connection with the Bengal endemic area to the west, and the spread north over China in epidemic form For that purpose the available data from 1900 to 1955 have been collected, and the annual death-rates per 1000 are shown in the chart (fig 2), so as to be comparable for India, Burma, Thailand, and Indo-China The chart also shows the years in which epidemics of cholera spread over China, of severity graded I, II, or III (Wu Lien-Teh 1932)

Grade III includes the most serious epidemics, in which the disease spread over nearly all China as far north as Manchuria and Korea Grade-I epidemics were limited to South China, and grade-II were intermediate, with involvement of Central China and the Yangtse valley In the remaining years there were no widespread outbreaks, and only a small mortality from the disease in the extreme south of China, bordering on the endemic area of Indo-China, and in ships coming from southern endemic areas

The Spread of Cholera from India to Eastern Asia

Before the data shown in the chart are considered, a brief summary must be given of the spread of cholera over Far East Asia in pandemics during the 19th and 20th centuries

The earliest was recorded in the latter part of the 19th century by John Macpherson (1872) But the most striking was that of 1840–49, described by N C Macnamara in his classical *History of Asiatic Cholera* (1876), and illustrated by a map in my *Cholera and its Treatment* (Rogers 1911) Cholera was then carried by sea to China, and spread inland across Central Asia to reinvade the Punjab from the west and Upper Burma from the north, contrary to the general rule The 1861–62 pandemic was also carried by the sea route to overrun China

Since the endemic areas of Assam and Bengal are contiguous with Upper and Lower Burma respectively, we must study the

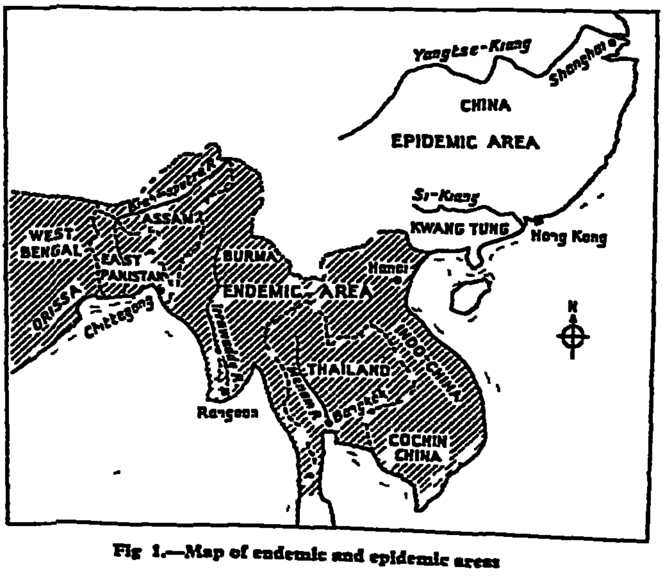

Fig 1.—Map of endemic and epidemic areas

MEAN MONTHLY VALUES OF WATER-VAPOUR PRESSURE (IN HG)

—	January	February	March	April	May	June	July	August	September	October	November	December
Rangoon (Burma)	0 576	0 618	0 704	0 803	0 900	0 905	0 900	0 900	0 900	0 898	0 780	0 622
Bangkok (Thailand)	0 691	0 839	0 909	0 954	0 992	0 969	0 942	0 963	0 951	0 915	0 851	0 688
Hanoi (Indo China)	0 413	0 499	0 561	0 717	0 907	0 977	0 977	1 022	0 918	0 726	0 620	0 517
Hong Kong (China)	0 390	0 387	0 493	0 620	0 785	0 886	0 915	0 915	0 842	0 650	0 493	0 405
Shanghai (China)	0 159	0 186	0 213	0 345	0 484	0 691	0 889	0 871	0 656	0 419	0 310	0 224

annual medical reports of Burma for evidence of cholera spreading eastwards from India This is limited by the absence of any good road or railway communications between Assam and Burma, to the north by a mountainous area blocking the east end of the Brahmaputra valley, and to the south from the Chittagong district of Eastern Bengal by hilly country Nevertheless a study of many annual medical reports of Burma reveals that some 300,000 labourers travel yearly to Lower Burma from Eastern Bengal, and they have been known to spread cholera during the spring rise in the incidence of the disease Such outbreaks of cholera in Lower Burma should be controlled by the annual inoculation of such dangerous immigrants

Moreover, although pilgrim traffic is on a much smaller scale in Burma than in India, there are a number of yearly festivals at the Burmese pagodas attended by some 280,000 pilgrims, who have frequently spread cholera outbreaks They also should undergo compulsory inoculation every year, in view of the striking success of that measure in India in recent years

Cholera Incidence and Meteorological Conditions

The data shown in fig 2, which include material failures of the monsoon rains, must next be studied in the light of recent experience in India to ascertain whether epidemics of cholera in East Asia can be foreseen in time to allow of their being controlled by measures that proved effective in India

The upper section of the chart reveals six years in which cholera epidemics of grade III spread over China from the south as far north as Manchuria The first of these epidemics, in 1902, originated in the great Indian epidemic of 1900, which, as usual, followed widespread failures of the south-west monsoon rains in June to October of the previous year The recorded deaths from cholera in 1900 in India were 797,273, or 3 72 per 1,000 of the population This epidemic involved Burma in the same year, during 1901 and 1902 it spread eastward over Thailand and Indo-China, and was still prevalent in southernmost China in 1903 Hong Kong, the Straits Settlements, and the Philippine Islands were also involved

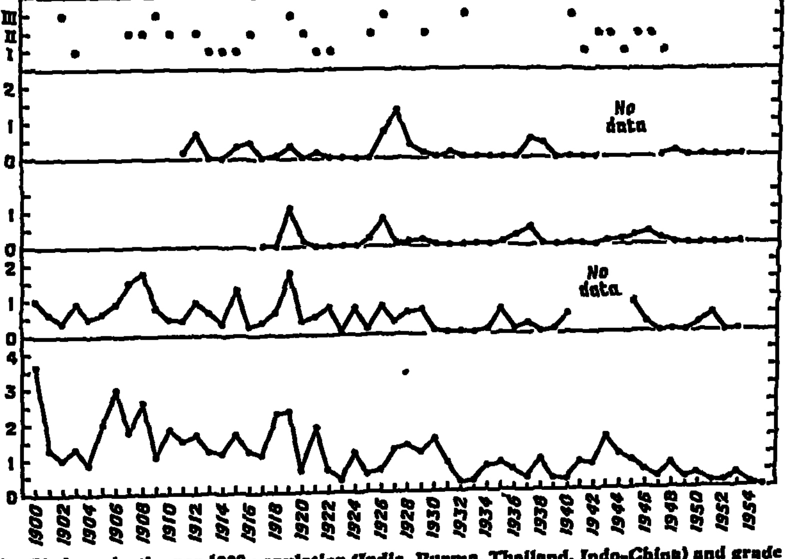

Fig 2—Cholera deaths per 1000 population (India, Burma, Thailand, Indo-China) and grade of epidemics (China)

In the 1906–09 epidemic, India was involved in 1906–08, with cholera mortalities up to 1 43–1 68 per 1000, and China had grade-II outbreaks in 1907 and 1908, culminating in a grade-III one in 1909 extending as far north as Manchuria once more Hong Kong, Singapore, and the Philippines were also involved It is noteworthy that in China the 1907 summer monsoon rains were deficient—a shortage that almost always precedes cholera epidemics in India by resulting in scanty drinking-water supplies during the succeeding annual spring rise in cholera incidence

In the 1918–20 cholera epidemic India showed the high cholera mortalities of 2 35 and 2 40 per 1000 in the first two years Burma had the high rate of 1 53 in 1919 and Thailand one of 1 13 per 1000, the highest of the past half-century, with 10,277 deaths from cholera In Indo-China the rate rose to 0 27 per 1000, and a grade-III epidemic once more spread north over China to reach Manchuria It continued as a grade-II outbreak in central and south China in 1920, and as grade I for the next two years in south China only, with absolute humidities of January and February of almost 0 400

The 1924–26 epidemic ran a very similar course to that of 1918–20, for the cholera death-rate rose in 1924 in both India and Burma and was followed by increased prevalence in Thailand in 1925 and 1926 and in Indo-China in 1926 and 1927, to reach the highest level in the series of years of 24,201 deaths, 1 34 per 1000, in 1927 This epidemic culminated in a grade-II epidemic in 1925 and a grade-III one in 1926, reaching as far north as Manchuria It was again aggravated by a water shortage, the annual rainfall in Shanghai in 1925 was 13 85 in , or nearly a third of the normal

In 1932 another grade-III epidemic affected China as far north as Manchuria, but was exceptional in not having been associated with high cholera prevalence in the countries to the south, except for a moderate rise of 1580 deaths, or 0 18 per 1000, in contiguous Indo-China However, Wu Lien-Teh (1932) records that the first cholera death of this year was on the unusually early date of April 26, and the outbreak at Shanghai, near the mouth of the Yangtse, spread to the south and also north to Manchuria The disease must have reached the great port of Shanghai by the coastal route from the south, as it has repeatedly been recorded to have done in the half-yearly reports of the medical officers at the Treaty Ports of 1870 to 1885, of which I have made notes This serious epidemic involved 23 provinces and 212 large cities, but the actual number of deaths is not recorded It was predisposed to by the low annual rainfall—a sixth below the average—and the occurrence of the first case as early as April indicates an early spring rise in the absolute humidity favourable to the early spread of the disease These factors may account for the fact that there was an epidemic though Burma and Thailand had not shown any material increase of cholera in the previous year, as had preceded the previous grade-III Chinese epidemics already described

In the case of 1940–47 China epidemics shown in fig 2, few data are available because the second world war had involved both Burma and China This period was accompanied by high cholera-rates in Burma in 1940 and 1941 and in India in 1941–45 In India famine conditions followed greatly increased prices of food, famine-stricken crowds wandered over the country The lack of data for the cholera deaths in the war years is illustrated by breaks in the curves in the chart

The general conclusion is that cholera epidemics in China are essentially due to the spread of the disease from the endemic regions of Eastern Bengal, Burma, Thailand, and Indo-China (in years of increased prevalence of the disease) across the southern border of China over greater or less areas of that vast country

Relation of Cholera Incidence in Burma to Meteorological Conditions

The incidence of cholera in Burma from 1877 to 1922, in relation more particularly to rainfall, is dealt with in my memoir (Rogers, 1928, pp 156–162) It is there recorded that in every one of the fifteen years in which the cholera incidence was 50% or more above the yearly average, the rainfall during the preceding south-west monsoon of June to September, or during the succeeding October to December, or during both periods, was seriously in defect Tables (Rogers, 1928, pp 147, 149, and 151) show that the same relationship holds good in the adjacent endemic areas of Eastern Bengal and Assam In all these areas the minimum cholera season is during the abundant rains of the south-west monsoon—e g, in Lower Bengal only 4% of the total annual cholera mortality is recorded at this season Exactly the opposite is the case in the epidemic areas to the north-west and west of Bengal, with absolute humidities below the critical point of 0·400 in the cold-weather months As in the endemic areas of Lower Bengal and of Burma to Cochin-China, the absolute humidity during the cold-weather months never falls to the critical level In these regions the annual rise in the cholera incidence starts in October to December, immediately after the cessation of the monsoon rains Hence the early failure of the monsoon and of the rainfall of the last quarter of the year results in the early and continued rise of cholera incidence in October and November, with high total incidence in the twelve months from October onwards Such years of high cholera incidence can thus be foreseen, though only very shortly before their occurrence From the extensive endemic areas of Lower Bengal, Assam, and Burma to Cochin-China, the epidemics spread to the west of Bengal over the epidemic areas of India and from South-East Asia northward over China, but only with the rise of the absolute humidity to well above the critical point of 0·400 in March to May in India and from late April onwards in China more particularly in the Central and Northern provinces This allows ample time for large-scale preventive inoculations to be used to protect China from the spread of cholera from the endemic areas to the south

Recent Cholera Incidence in India, South-East Asia, and China

The incidence of cholera has declined since 1947, with the exception of a rise in Burma in 1951 following deficient south-west monsoon rains The great decline of the disease in India has been shown to be due to compulsory inoculations on a large scale, but this explanation does not apply to Burma, where the latest data from 1947 to 1956 show an average of only 202,000 annual anti-cholera inoculations—very small figures in proportion to the population, as compared with those in India during the same period Moreover, the data show clearly that in years of low cholera incidence in Burma the inoculations fell to an average of under 50,000, this indicates that the inoculations were used extensively during outbreaks only when it was too late to control them

On the other hand, recent years have shown an unusual number of good monsoon rains, unfavourable to enhanced cholera incidence, in both India and South-East Asia, which cannot be expected to continue much longer Moreover, my studies of all the available Indian data from 1866, now extending over ninety years, show that very low cholera incidence in one year is liable to be followed by high rates whenever deficient monsoon rains favour a recrudescence of the disease, so preventive measures must be considered

Control of Cholera in the Endemic Areas with the Prevention of Spread over China

All sanitarians will agree that the ultimate control of cholera depends on the provision of safe drinking-water to the million or so villages of India and probably still larger numbers in South-East Asia and China The number of decades—or should it be centuries ?—that will be needed for that purpose is anyone's guess Meantime the authorities should consider the application to Far East Asia of the large-scale compulsory inoculation measures that have already met with success in India

The principles of the new plan of control are simple, but their application will vary to some extent with local conditions Thus in India the main task was the yearly inoculation of some twenty million pilgrims, who travel long distances through cholera-infected districts to attend religious festivals, become infected, and carry the disease back to their own villages On the other hand, there is very little spread of cholera by coastal sea traffic, which is a feature of its extension into China from the south All immigrants into China from the more southerly endemic areas should be inoculated against cholera at least a week before they are allowed to enter Chinese territories, preferably before embarking for the journey In the case of ocean-going steamships, this is probably already provided for Its great value is demonstrated by the long established inoculation of vast numbers of pilgrims to Mecca, which has put a stop to the spread of pandemics by them to South-East Europe, which were a feature of the 19th century A more difficult problem is presented by the extensive movements by coastal traffic of small vessels and by the large boating population in the estuaries of the great rivers of China Quarantine measures have for long been in use in Chinese ports, and judging from recent Indian experience, the advantages of regular large-scale anti-cholera inoculations are very soon realised by the people and have even led to their clamouring to be inoculated against cholera before undertaking journeys in cholera-infected areas This should obtain still more if it also avoids quarantine measures, which are far more unpopular

The appearance of cholera cases in vessels arriving in the more southern Chinese ports used to be a regular annual event, but the most serious epidemics have usually been due to overland spread in years of high cholera incidence in the endemic areas, as shown earlier It is also on record that quarantine methods have always failed to avert such spread overland The Chinese Government now have control of the northern portion of Indo-China, this will facilitate their control of the extension of cholera over southern China But to avert the more serious epidemic spread it will be necessary to keep a close watch on the development of high incidence of the disease in the cold-weather months, in Burma more especially, following deficient rainfalls during the preceding south-west monsoon and autumn period This can now be done, owing to issue in recent years of the weekly bulletins of epidemic diseases by the World Health Organisation

But to strike at the root of the problem it is essential that the endemic regions of Burma, Thailand, and Indo-China should adopt the successful Indian plan of enforcing compulsory inoculation every year of all pilgrims, immigrants, and other travellers from without and within their territories This measure will require about a decade to bring about its full effects But success should result, not only in the control of serious outbreaks in the territories concerned, but also in the prevention, in future years with extensive failures of the summer monsoon rains, of the pandemic spread of cholera over both Asia and Europe One more scourge of humanity will then have been brought under control by medical science

Conclusion

The incidence of cholera during the last half-century in the endemic regions of South-East Asia, and its epidemic extension northwards over China, have been studied The adoption is advised in Far East Asia of the large-scale compulsory inoculations, which have already greatly reduced cholera mortality in India during the past decade

I desire to acknowledge my great indebtedness to Sir Graham Sutton for supplying me with extensive meteorological data, to Dr Wu Lien-Teh for the loan of his valuable papers on cholera in China, and to Dr Charles Wilcocks and Mr Cyril C Barnard, both of the London School of Hygiene, for much help in obtaining literature on the subject

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Points of View

MEDICAL PRACTICE IN A CHANGING SOCIETY*

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New problems and new solutions are continually arising in our society Nothing is static Medical practice influences social conditions, and these in turn affect medical practice

Liberalism and Socialism

In the past half-century, side by side with the advances of science and their effects on our way of life, there have been two less tangible developments which have directed the policies of government and of all who have power to influence our thoughts, our ethics, and our morals These are the acceptance of liberalism—using that word in its widest sense—and the partial acceptance of socialism

By liberalism I understand the recognition of the value of the human personality—the belief that the individual human being should be free to exercise his peculiar abilities and energies, and that everybody has equal right to this freedom, regardless of social class or race To put it shortly, liberalism insists on the brotherhood of man and is inspired by the Christian ethic Not only has liberalism been accepted and cherished by this country, but it is generally accepted as the guiding principle of what we at present call Western culture It is in no way a new principle, but it was not generally accepted fifty years ago Today, though the best way and rate of implementing it is still a matter of debate, all three political parties in this country accept it without question The educational reforms have been inspired by it, the gradual narrowing of class distinctions is the result of it, and the gradual loss of the privileges of birth, and to some extent also of wealth, are the direct results of its acceptance

In strong contrast to liberalism, with its insistence on the paramount importance of the individual, are the principles of socialism These lay stress on the importance of the group, of the community, of the herd, and insist that the direction and control of our way of life should be in the hands of the community and ultimately of the State, the interest of the individual being secondary The socialist idea has been partially accepted as essential for successful government in these times of intense economic competition between nations Its progress is largely the outcome of the second world war when the best use of all our resources was a necessity, and centralised direction and control was the only means of coordinating effort From these war experiences arise the almost obsessional clamour for planning, with the risk of totalitarianism and an oppressive bureaucracy

Between the doctrines of liberalism and socialism this country continues to compromise with its traditional skill

One present result is the Welfare State, with its National Health Service, retirement pensions, insurance against unemployment and accident, subsidised essential foodstuffs (especially for pregnant mothers, infants, and schoolchildren), free education, holidays with pay, legal assistance, housing subsidies, and so on And to pay for all this we have crippling death duties, supertax, and a very high rate of income-tax especially on unearned incomes, which have removed any lingering vestiges of the feudal system and have almost abolished the landed aristocracy

Science and Technology

The most obvious effects of science and technology on our standard of living and way of life come from the application of metallurgy and chemistry and electronics in the factory and in the home But perhaps the greatest influence on our lives has been the development of what are generically termed communications—facilities for more rapid travel, the telegraph, telephone, wireless, and television, the cinema and the daily press Through the printed or the spoken word, by visual demonstration, or by seeing for himself, each of us is kept closely informed of what is happening in any part of the world, and these events crowd on us daily or hourly A person can no longer confine his interests to his immediate surroundings no longer does his family and his work group provide him with all the incentives and reasons for his physical and intellectual activities Fifty years ago he was the member of a family and of a village community, or the citizen of a town, but now he is being gradually forced to see himself as a citizen of the world, who must share in the problems of his fellow men, no matter where they live or to what race they belong The raw materials required in his work, essential for his continuous employment, may come from many countries and continents, and in order that the products of his work may be sold there must be not only a demand but also purchasing-power in countries that until recently he had never heard of In the words of A H Compton, chancellor of Washington University in St Louis

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* From a Pfizer postgraduate lecture to the Glasgow faculty of the College of General Practitioners

> " One important change in our mode of life is that the contacts of person with person are becoming more frequent and more extensive This growing interdependence is a part of the process of becoming more civilised At present we find ourselves becoming members of a world community Thus the community to which one belongs is extending more and more widely until already in many of its aspects it embraces all of mankind " [1]

The influence on our way of life of these ethical and political principles and of the discoveries of science has been great, and is still active The conditions are constantly changing and there is no sign of any slowing of the rate of change—no indication that we are nearing a stage of stability and security

Changing Foundations of Medical Practice

Science and technology have affected the practice of medicine as much as they have affected social conditions There have been great advances in preventive medicine, in diagnostic accuracy, and in therapeutics, and the general picture of practice has changed both for the family doctor and for the specialist

More perhaps than any others, two advances are responsible for this change in the picture one is the control of infections by means of the sulphonamide drugs and the antibiotics, and the other the increasing range of surgery, largely due to the dramatic improvements in anæsthesia By control of infections and by successful surgery we can remove many of the basic causes of ill health or of death , and this should, of course, always be our aim, though for most of our patients we still have to rely on the treatment of symptoms and any other aid we can offer while they recover their health and capacity, or fail to do so

Besides the advances that enable us to remove the causes of ill health, there are others that help us to control abnormal processes or so modify the symptoms of disease that our patients can more readily recover, or at least continue in gainful occupation In this category I need only mention the hypotensive drugs, the anticoagulants, the analgesics, hypnotics, sedatives, tranquillisers, and diuretics, and we look forward to the further development of treatment by synthetic hormones

In diagnosis also, scientific advances have been impressive The most important are the analyses of biochemical processes, in which the use of radioisotopes have proved a valuable tool More obvious perhaps has been the development of radiodiagnosis to disclose the structural causes of disturbances of functions The use of X rays and contrast media and of cardiac catheterisation allowing the clinician to define the lesions in diseases of the heart and circulation with the accuracy necessary for cardiac and vascular surgery, and similar developments in the diagnosis of diseases of the lungs and bronchi are essential to the increasing successes of thoracic surgery Less dramatic perhaps, but no less intellectually satisfying are the advances being made by the hæmatologists

The use of the scientific method has made the practice of medicine—preventive, diagnostic, and therapeutic—become more precise For many of our patients we can now do much more to save or prolong their lives or to help them to live with their abnormality

An analysis of clinical medicine stated by Wilfred Trotter some years ago is, I think, worth recalling at this time He pointed out that clinical medicine includes an experimental science—a strictly scientific discipline—which requires that no conclusion be reached till the evidence is complete, but that for the most part the practice of medicine is composed of applied science, and a practical art As I have indicated, the application of scientific discoveries to clinical medicine is a part of practice that is growing now at an increasing rate But there remains the third constituent—the practical art by means of which we care for our individual patients, based on the experience of similar situations, on a cultivated intelligence, and on a knowledge of human beings For its successful exercise, it requires sympathy with human suffering It is founded on the personality and character of the practitioner and it cannot be taught, though it can be greatly encouraged by the example of teachers and senior colleagues The same now as it was in the days of Hippocrates, this personal component of clinical medicine will be required in the future as in the past

The Individual and the Changing Society

Much has been written of late years about the absence of real happiness, joy, and satisfaction among our people—in spite of the Welfare State, in spite of better physical health, in spite of all the labour-saving and increased leisure that applied science is giving us From a variety of standpoints, the writers all agree that the situation is serious and that it results from the rapidity of the change in conditions of our society They point out also that these changes and developments, in so far as they are the result of conscious design, are failing to produce the very benefits intended—namely, a fuller and a happier life for each individual

Man is the most highly developed member of the animal kingdom and it is his nature to be continually seeking outlets for his endeavours, he cannot remain static, but feels an urge to progress and to develop the potentialities of his personality For this he needs freedom At the same time he is a social animal and can develop successfully and happily only in cooperation with other human beings, other personalities He is assisted in this by the advances in science and technology which enable the life of each to become more closely identified with the life of mankind, but his ties to his family and to his local community have become looser

At the beginning of this century the codes of behaviour acquired in the family circle and later at school and elsewhere were based on a long tradition, in which religion and pride of place in the community played considerable parts People looked forward to a life in which these foundations gave stability, their futures were relatively secure, and their relations with their fellows followed a recognised pattern Wider educational horizons have shaken the trust of the adolescent in the values and traditions of the family It has been pointed out that the parent-child conflict is intensified during periods of accelerated change, and as Eisenstadt [2] puts it

> ' The transition from family to total society is necessarily fraught with severe emotional difficulties, as it necessitates redefinition and transformation of the individual's role expectations '

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[1] Compton A H *Proc. roy Instn G B* 1955, 35, 788

[2] Eisenstadt, S N From Generation to Generation London, 1956

These emotional difficulties affect both the child and the parents

Instead of receiving their moral, ethical and behaviour values from the family and the local community, adolescents, and adults also, now get them from many different sources—trade-unions, the Press, wireless, cinema, age-groups, clubs, the Army, and so on These present a great variety of experiences from many countries with various cultural standards and competing values, many of which cancel out each other, and man lacks the psychological certainties of custom and precedent to guide and steady him

In his *Diagnosis of our Time*, Karl Mannheim [3] says

> "We should not forget that moral codes, like legal regulations, are devices for moulding human behaviour If we have so far been able to do without institutionalized control in the moral field, this is mainly because the ethical standards of everyday life have been created for the most part by trial and error, and transmitted by anonymous tradition But trial and error only work as long as social conditions favour unconscious selection that is, as long as changes take place so gradually that unworkable norms are sloughed away in the course of time *This is not what is happening today* The speed of transformation is surely too great to permit unconscious experiment and selection The individual is lost in an invisible society, and is too weak to invent new norms for himself The result is moral chaos in which religious standards, family traditions and neighbourly ethics are losing ground without being replaced by other principles"

and again

> "The most fruitful methodological device in science, namely to adjust if necessary our whole system of thought to the ever-broadening sphere of experience, becomes when applied to human life and moral issues, the greatest predicament of modern man By developing the same kind of dynamic rationality in the moral world, modern man tends to lose a firm basis on which to stand Whereas in some prominent individuals this falling into the abyss of the self without reaching the bottom presents itself as a grandiose struggle, in the average man the very same dynamics lead to a frivolous attitude of believing in nothing and to an endless craving for new sensations"

The average person, then, is suffering from the loss of the sense of security that arises in the absence of accepted standards of behaviour and of moral codes, but the changing social conditions are interfering also with the human urge to assert his individuality and to contribute his own peculiar talents in cooperation with his fellows Even a partial acceptance of the principles of socialism induces uniformity Man is moulded to a pattern by the education in the local-authority school, and in his work he must conform to the dictates of his union, the decisions of which he may have little, if any, say in determining Service with the Armed Forces emphasises the same trend The more the central planners are able to regulate our lives, the fewer are the opportunities of men and women to develop their talents and personality, and to progress

Sir Alexander Gray [4] has expressed this concisely

> " and Planning, as now understood, means among other things the removal from the decision of the individual or the electorate to the decision of the expert who is, by definition, always right"

and he concluded

> "I suggest to you, hesitatingly and for your consideration, that the Welfare State, in its unbounded benevolence, may find itself driven to a degree of regimentation and control which would make it in essence a government at least mildly totalitarian in character"

Though adoption of the principles of liberalism and socialism, and the advances of science and technology, are bringing enormous improvements in man's way of life and in the social conditions of this country, these are largely material and have been accompanied by a loss of stability and of the traditions that gave to each individual a sense of security The average person feels frustration when hemmed in by regulations he becomes restless and can find no outlet or relief It becomes harder for him to cooperate with those with whom he is in contact in his work, and even in his home These mental stresses so affect him that sooner or later his efficiency and his bodily health may suffer Before long he seeks the help of his doctor

The Changing Practice of Medicine

We saw how the advances of science have enabled us to be more precise and definite in the diagnosis of disease processes and to apply curative or corrective therapy to an increasing degree over a continually expanding field It gives us intellectual satisfaction and professional confidence to be able to help those patients in whom the disturbance to health and well-being can be so dealt with But perhaps we are, in consequence, less ready to spend our time and our energies on those patients whom we cannot help so directly, so dramatically We may be tempted even to be less sympathetic towards them It is disturbing to hear so often from members of the public "I didn't tell the doctor about that, he seemed too busy", or "I told the doctor, but he paid no attention to that"

It is well to take for granted that every patient who decides to visit a doctor feels fear or apprehension in some degree Only rarely is it fear of death, but usually there is fear about inability to hold down a job, or to manage the household, or to look after the children, or perhaps merely to get the best out of life, and the mother's worry for a sick child can produce a strong and deep emotional upset It is also a good rule in clinical medicine never to be satisfied with what has been done for a patient until the evidence is sufficient for a prognosis to be given, even if it would be unwise to state it The prognosis is the answer to the question, often unspoken, "What does this mean to me ?" or "What does this mean to my child ?" Exclusion of organic disease does not in itself justify the diagnosis of a stress or psychogenic cause If such a cause exists, the prognosis will depend on whether or not it can be eliminated or its effects modified, and for this to be possible it must be tracked down No-one is more competent to do this than the family doctor with his previous knowledge of the patient, of the home, and of the other members of the family Moreover, the therapy required for most of these patients needs no psychiatric specialist or expert training, common sense and a knowledge of the family and their environmental conditions are more valuable, and above all human sympathy and a desire to help and serve our fellow human beings—the essence of the practical art of medicine

The obvious difficulty is, of course, that all this takes up precious time which the practitioner may feel would be better spent on patients suffering from more definite disease and for whom we can do something specific and up to date But often more time can be found by better organisation of the work

For example, P M Higgins [5] describes how the institution of an appointments system and a shift system for himself and his four partners eased the pressure on their time and accommodation J G Ollerenshaw [6] shows how office work can be handed over to a receptionist and secretarial staff, and better use made of the services provided by the local health authority. Many practitioners, I think, are unaware of the help their local authority is prepared to give, and the more cooperation he establishes with the hospital service and his local authority the more time he will have to give to those patients whom he can best serve.

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[3] Mannheim, K Diagnosis of our Time London, 1943

[4] Gray, A *Univ Edinb J* 1952, 16, 146

[5] Higgins, P M *Lancet*, 1957, i, 680

[6] Ollerenshaw, J G *Med World*, 1957, 86, 251

If the little enough time now available for leisure and recreation is not to be curtailed, clinicians should rid themselves of every task that can be performed as well, if not better, by others. In this way only can they meet successfully the challenge of a changing society. I must add that the most obvious means of getting more time to deal properly with the fears, apprehensions, and mental stresses of our patients is for each doctor to have fewer patients for whose care he is responsible, and this some doctors are doing.

Our profession has been accorded a peculiar privilege that distinguishes us from members of all other professional groups. This privilege has been given to us not by the State but by the people. They trust us and confide in us, and they ask us to relieve them of the burdens that unaided they find are too much for them. Because of this privilege, there is much more in the practice of medicine than the application of science. No matter how great the advances still to be made by the employment of the scientific method, there will always be a need for the practical art of medicine.

Conclusion

At present we are so busy preventing, diagnosing, and treating diseases that we have too little time left for treating our patients, for caring for them and relieving them of their burdens. But our patients are in greater need now than ever before of the care and devoted service that we have been especially selected and educated to give to them.

Medicine and the Law

Artificial Insemination not Adultery

CAN a wife who has borne a child as a result of artificial insemination be said to have committed adultery? This question came up for consideration recently in the Scottish Court of Session on the hearing of an action for divorce brought by the husband.[1] In a reserved judgment given last week, Lord Wheatley ruled that artificial insemination does not in law constitute adultery.[2]

The husband and wife had not lived together since March, 1954. In July, 1955, the wife gave birth to a girl. Her claim was that the child had been born as the result of artificial insemination through a donor, and that this was not adultery as the Law understood it. The husband maintained that he had never agreed to this course if in fact it ever took place, and that such a general defence was irrelevant.

Lord Wheatley, who described the case as unique in the annals of our Law, said that there were manifestly grave moral, ethical, social, and personal considerations involved in the practice of artificial insemination. It was almost trite to say that a married woman who was artificially inseminated in order to have a child who would not be the child of her marriage had committed a grave and heinous offence of contract of marriage, but the question for him to determine was not the moral culpability of such an act but whether it constituted adultery in its legal meaning.

His Lordship said that, having examined the Law of England on adultery and having found nothing to persuade him that the Law of Scotland was not the same on the subject, and having studied the opinions expressed by judges in other countries and in textbooks, he had reached the conclusion that artificial insemination did not come within the definition of sexual intercourse as understood by Scots Law. "Just as artificial insemination extracts procreation entirely from the nexus of human relationship in or outside marriage, so does extraction of the nexus of human relationship from the act of procreation remove artificial insemination from the classification of sexual intercourse. . . . it follows that artificial insemination by a donor without the consent of the husband is not adultery as the Law interprets that term."

This judgment is not binding on the English courts, but it will undoubtedly have great persuasive value and is very likely to be followed if the matter ever comes up for consideration in England. Although the two legal systems differ in some important respects, there is a tendency for the courts of both countries to follow each other's decisions if possible. Lord Wheatley's view that there cannot be adultery without actual sexual intercourse is in line with English judgments on the nature of adultery. Thus manual gratification by a wife of another man's sexual organs has been held not to be adultery, although a breach of the obligations of marriage. The distinction between adultery (which is a ground for divorce) and various other breaches of the responsibilities of marriage (which are not necessarily a ground for divorce) is cardinal to the whole subject, and should not be overlooked in the debate which will no doubt result from Lord Wheatley's judgment.

Public Health

Atomic Safety: a Report after Windscale

AFTER the accident at Windscale no. 1 pile last October, a committee, under the chairmanship of Sir Alexander Fleck, was asked "to review the organisation within the Authority as a whole for control of health and safety and to make recommendations." A summary follows of the committee's findings and recommendations.[1]

The accident revealed latent public anxiety about the risks of atomic-energy work. The precautions already applied were very elaborate, the aim must be to err on the side of caution. The accident revealed that the Authority's organisation was inadequate, but improvements in it must be supplemented by clarifying the relations between the many Government departments concerned with atomic safety, by coordinating the activities of these departments, and by building up the Atomic Energy Office to enable it to play the leading role. The measures needed for safety were formulation and observation of appropriate codes of practice, with numerical limits established by experiment and with monitoring of plant and operations by safety staff.

The hazards to be considered were exposure of workers to radiation, loss of control of a nuclear reactor (including unintentional assembly of critical masses), and discharge, as effluent or by accident, of radioactive matter.

The Authority's three groups (industrial, weapons, and research) should collaborate on problems of criticality, to ensure that a critical mass of material (i.e., that which leads to a nuclear reaction, giving rise to heat and fission products) was not assembled accidentally.

The committee agree with the Authority that an independent board should be set up to license nuclear reactors, but at present the only people competent for this were on the Authority's staff, and it must remain a long-term objective.

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[1] *Times* Dec. 6 1957.
[2] *Ibid* Jan. 11, 1958.

[1] The Organisation for Control of Health and Safety in the United Kingdom Atomic Energy Authority. H.M. Stationery Office. Cmnd. 342. Pp 28. 1s. 3d.

Decentralisation of management in the Authority meant that health provision was not uniform The report endorses the Authority's decision to set up a committee responsible for overall supervision of all matters of health and safety The management of health and safety in the factories of the industrial group should be integrated into a single section responsible directly to the works general manager The health and safety manager should be a physician of consultant calibre, with sound training in industrial health, special knowledge of the health aspects of radiological protection, and some knowledge of the associated problems in physics, chemistry, and engineering If such a man could not be found, the best alternative would be a physicist with knowledge of the biological aspects

One of the most important points emerging from the committee's review was the serious shortage of people with the necessary qualifications in medicine, radiology, health physics, and nuclear physics and engineering Health and safety should be made an attractive career, with appropriate salaries and the provision of proper instruction The Authority "should assume responsibility for building up the national supply of these health and safety specialists, who will be required in ever increasing numbers" The specialised training provided by the Authority should take eighteen months, full time, including up to nine months' study of radiation physics The training should merit a new professional qualification The Authority should also recruit and train, on the job, the new special works medical officers, and offer training to public and industrial health workers, sanitary and water engineers, and the police This training should be carried out in a national centre, which would also cover the health and safety aspects of the use of isotopes in medicine, agriculture, and industry

The Authority should review the procedure for the publication of information about accidents, and coordinate the site emergency procedures and bring them to a uniformly high standard in all units

Londoners Last Year

A preliminary report on the health of the county of London in 1957 has been issued by Dr J A Scott, the medical officer of health The death-rate, at 11 2 per 1000, was the lowest (except for 1954) since 1948 Mortality was light in the mild first quarter, but there were 2000 more deaths than usual in the December quarter and the number of deaths from respiratory disease was twice the average There were an estimated 350 cases of poliomyelitis, with 12 deaths Tuberculosis mortality fell from 0 14 to 0 11 per 1000, and there were fewer notifications 23,000 children were vaccinated with B C G

The birth-rate rose, for the first time since the 1947 peak Infant mortality was 0 35 per 1000 births—the lowest on record, except for 1956 46% of pregnant women and 87% of children under a year attended the L C C antenatal clinics

The Third Quarter in England and Wales

The Registrar General has issued his report[1] for the quarter ending Sept 30 last. His figures for births, deaths, stillbirths, and infant mortality confirm those given previously[2] Other details include

Population and life expectancy—Abridged life tables are given, based on the mortality experience of 1954–56 The expectation of life in years for males (females in parentheses) is 67 6 (73 1) at birth, 68 6 (73 7) at 1 year, 50 3 (55 3) at 20, 31 4 (36 2) at 40, 15 0 (18 7) at 60, and 5 2 (6 2) at 80 Population tables show that males outnumber females in all age-groups up to 30, thereafter women outnumber men The total population at June 30 was estimated at 45,043,000, including 2,070,000 men and 3,196,000 women aged 65 and over

Infectious diseases—The death-rate was 96 (91) per million from tuberculosis, 392 (267) from pneumonia, and 9 (3) from poliomyelitis (figures for third quarter of 1956 in parentheses) Smallpox caused 2 deaths, the first since 1953

In England Now

A Running Commentary by Peripatetic Correspondents

With some thousands of other citizens I spent last Wednesday evening "just messing about in boats" At Olympia there were hundreds of boats, large and small, round and flat, black and white, glass (yes glass) and wood, driven by air, oar, and diesel They must have knocked the wall down to get some of them in, or else built them there complex rigging soared skywards and was lost in the smoky haze around the second-floor gallery At the other extreme sailing dinghies shrank to pram dinghies and canoes for achondroplasiacs finally there was a sort of folding boat that could be carried in one hand like a bag Doubtless there was an inflatable boat somewhere that fitted snugly into the vest pocket Lifeboats, patrol-boats, and even the Armed Services were represented, one remarkable boat had rotors fitted with which the thing could fly in the air But I didn't see a single raft True there was a *minute canoe about 8 in across in which some madman* crossed the Atlantic But no rafts shades of Kon Tiki and Jerome K Jerome Or maybe rafts are just a little bit *too* easy to make yourself in the back garden and not worth plugging A splendid nautical atmosphere was created by the sounds of distant breakers and B B C seagulls coming out of the diffusion system

The clientèle looked rather dull just like the people that go to the Radio Show, the Photographic Show, the Motor Show, and even our little Show There must be a nucleus of people that attend all exhibitions for the heck of it without being especially interested why of course there's me for a start But the odd beard sprouting a curly pipe and covering a duffle coat suggested that some yachtsmen were present, and I heard one splendid salty character, a lifelong yachtsman to the tips of his bushy eyebrows, remark "Quite a good show all round—but too many d——d engines"

After an hour or two one gets a surfeit of seafaring gallery after gallery of stoves, lamps, rudders, binnacles, and blocks stretch ahead The salesmanship could learn a thing or two from our little show nobody invited me to heave to and prepare to board, and I couldn't even cadge a sample tin of waterproof paint So after taking on ballast at the canteen we luffed windwards to the exit feeling slightly seasick

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After the effects of turkey and cigar amblyopia had abated I settled down to analyse our Christmas-card series 11% boasted holly, 11% Father Christmases (3 with reindeer and 3 using more modern means of transport—car, train, and sputnik) 10% showed a winter scene, but the orthodox seasonal balance was upset by 1 autumnal picture and 1 view of summer in Sydney (Australia) Food (mainly puddings with some of the 11% holly stuck into them) formed 7% Coaches and carol-singers were surprisingly poorly represented (3% each) and robin redbreast was a melancholy single entry Angels (3%—*1%* with tenor saxophone), *flowers* (4%), and simple unheraldic crests (4%) were significant The most bizarre single entries are not included in the present series, but they included an etching of Frankfurt am Main, a blonde hanging up nylon underwear, and a photograph of a Nigerian woman fishing in the Limbe River We shall have to wait till next year to see whether these are statistically significant

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One of the pleasantest English sports is catching trains It is so democratic And it has all the thrills of surprise and suspense It induces such sympathetic participation in the spectators Only the most antisocial refuse to enjoy the triumph of the train-catcher Rarely, you get the exquisite sensation of watching an artist *How unruffled he is How elegant* and perfectly coordinated are all his movements as he darts through the barrier and springs lightly on to the moving train You sink back into your seat with some of the afterglow that *follows Spectre de la Rose*

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[1] Registrar General's Quarterly Return for England and Wales Third Quarter, 1957 H M Stationery Office, 1957 Pp 24 1s 6d

[2] See *Lancet*, 1957, ii, 887

As a warning to would-be emigrants to Canada I should like to quote from our railway by-law no 99, approved by the Board of Transport Commissioners for Canada and sanctioned by His Excellency the Governor-General-in-Council

> No person, except a servant or agent of the Company in the performance of his duty, shall open any vestibule door or stand upon the steps or platform of any car while it is in motion, or entrain on or detrain from, or attempt to entrain on or detrain from, any such car while it is in motion

And in case anyone may think that a railway by-law means nothing, like no-smoking in English trains, they make it physically impossible to do what the by-law prohibits Bars of steel lock all the doors before the train moves

On board the train your safety is still the commissioners' main concern, even if you have villainously boarded the train without a ticket

> Every passenger who refuses to pay his fare or produce and deliver up his ticket upon the request of the conductor, may, by the conductor of the train and the train servants of the Company, be expelled from and put out of the train with his luggage at any usual stopping-place, provided that the conductor shall first stop the train and use no unnecessary force

The by-law that prevents you from leaping on to the moving train saves you from being flung off it, without your luggage, at some uninhabited spot Too many romantic souls think of Canada as a wild, lawless, rough-riding, sharp-shooting territory If train-catching is your sport, you'd better stick to the Euston Road

* * *

In the West of England hospital where I was reared the loudspeaker caller system for members of the staff is unknown, and before I came to St. Euphonia's I had only come across it in American films

It has various aspects that fascinate me There is the Voice From Heaven impression. This feeling of being personally called to Judgment every few minutes wore off after a while However, I still sometimes give an involuntary shudder when I hear my name called in a voice of doom, from outer space as it were

The impression that has lasted, on the other hand, is that of being part of a cosmic game of Happy Families "Calling Mr Sparks, the Electrician", or "Calling Mrs Potts, the Domestic Supervisor", never fail to put me in mind of the game I used to play as a child. It is a great pity that there is no way of reciprocating these demands over the loudspeaker "Have you got Mr Chips, the Carpenter?" "No, but have you got Mr Wrench, the Engineer? *Thank* you, *and* Mrs Wrench, the Engineer's wife? *Thank* you"

After all, the normal working of the hospital could always carry on with coloured lights

* * *

Last week one of our elderly patients, after an operation for an upper femoral fracture, showed evidence of basal lung congestion, and his sputum was sent to the laboratory for examination The report came back "The carton contained matchsticks" Orthopædic surgeons have gained many a nickname in the past fifty years—carpenters and monumental masons among them Now I know why

* * *

It's µ by name, but what by nature?
A line, you say? Diameter will do
Erythrocytes are 7µ, God bless 'em,
Mm divided into 7 thousandth parts
Cu µ is million millionth of a m(i)l
µl a litre's millionth is,
And µ of g, a thousandth milligramme

Micron or microgramme, it's all the same,
A thousandth of a thousandth part. A µ!
Pass on the sign from lip to lip,
For don't expect to find, my son,
This measure µ defined in books Eheu

Letters to the Editor

SURGERY OR RADIUM FOR CANCER?

SIR,—It is with regret that we notice that Professor McLaren and his colleagues (Jan 11) are using our recent communication as an occasion for reopening the old battle between radiotherapy and surgery in the treatment of cancer This battle may have been necessary once, but there can be little doubt that radiotherapy has become established as a therapeutic agent of immense value Today, therefore, there should be no prejudice or partisanship in the treatment of cancer—particularly carcinoma of the cervix, where it is of vital importance to the patient not to fall into the hands of either a surgical or radiation enthusiast, since each will use the method he knows best, and this may by no means coincide with the patient's best interest. One of the main functions of the joint clinic, the work of which has been reported, is to safeguard the patient against the risk of such misguided enthusiasm and ensure that she receive the most appropriate treatment, whether surgical or radiation, under the best conditions

Our object in reporting the work of the joint clinic was.

(1) To show that surgeon and radiotherapist can work in harmony as a team under ordinary hospital conditions
(2) To give some idea of the usefulness of such a clinic as reflected by numbers and types of case referred to it.
(3) To determine the advantages, if any, to the patient of the cooperative services thus made available.

To this end we compared the methods used and the results of treatment before and after 1944

It was not our aim or purpose to "do justice to surgery" or to "mention modern surgical results" There is already a wide literature on these themes and we would specially commend to Professor McLaren and his colleagues' attention Kottmeier's[1] analysis of surgical and radiation results, in which he shows convincingly that, with comparable clinical material, radiotherapy gives results equal to those claimed for surgery by Meigs and others Because we were conscious of our poor results in stage I (60·4% at 5 years), we undertook the "manœuvres" commented on by Professor McLaren—not, as he claims, to boost our radiotherapy cures to the detriment of surgery, but rather to boost our own morale It is always a cause for humiliation and self-searching if one's results are worse than those claimed by other workers The purpose of the discussion quoted by Professor McLaren was to show that under other and more fortunate conditions we, too, might have attained the 70% 5-year survival rates achieved by other workers which would have substantiated more firmly our statement that "It therefore seems that radiotherapy is not only undoubtedly the correct treatment in inoperable cases, but also usually the preferable treatment for operable cases" This statement forms the substance and flesh to be found on the seasonable but scrawny bird mentioned by Professor McLaren. Our statistical turkey was both home plucked and killed, since all the statistical tables were drawn up by one of us (C. A S) in the hope that our conclusions would not be befogged by the use of a multiplicity of incomprehensible statistical terms, usually much in evidence when unpalatable facts have to be obscured

We would summarise by repeating that our opinion based on our experience since 1944 is that in our hospital the results in stage-I cases (60·4%) submitted to radiation treatment compare well with those obtained when the Wertheim operation is performed (65·1%) In these circumstances we customarily recommend radiotherapy to our patients with carcinoma of the cervix (with the exceptions listed in our paper) To be able with confidence to offer a patient the opportunity of avoiding a major mutilating operation, we regard both as a gesture in the best tradition of medicine and as a happy reward for our labours over the past years

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[1] Kottmeier, H L *J Obstet Gynaec., Brit. Emp* 1955, 62, 737

Chelsea Hospital for Women, London, S W 3

J B Blaikley
M Lederman
C A Simmons

A DISTRICT MENTAL HEALTH SERVICE

Sir,—The Worthing Experiment, with an outpatient and domiciliary psychiatric service, described in your issue of Jan 4, is so obviously a step in the right direction that its success was assured We are particularly interested in the extensive use made of outpatient electroconvulsant therapy, since, for many years, we have regarded this procedure as the only method of substantially reducing the need for mental-hospital admissions

The Sheffield Mental Hospital, with its 2089 beds, has, since the last war, been responsible for a catchment-area population of a million people—a ratio of 2 beds per 1000, compared with 3–5 per 1000 for the country as a whole Admissions have of necessity been restricted to severely disturbed patients for whom outpatient treatment is inadvisable But it was fortunate that in 1942 outpatient electroconvulsant therapy first became practicable, and since then, the Sheffield Hospital has maintained an active unit which, in recent years, has provided up to 1000 treatments a year with satisfactory results in the moderately severe case of depression which could not be admitted because of shortage of beds A special treatment-session is reserved for geriatric patients

If it is estimated that the gross incidence of psychosis in the community is 9 per 1000, or 1800 cases in a 200,000 population, not more than a third of these will probably require inpatient treatment and not all in the same year

We therefore applaud the results achieved by Dr Carse and his colleagues, which amply support their plea for expansion of outpatient facilities in psychiatry It would seem that a unit of the Worthing type should be provided for each 200,000 population, and, until an effective substitute for modified electroconvulsant therapy can be found, each unit should be able to provide 30 to 40 treatments per week

Middlewood Hospital, Sheffield

F T Thorpe

Sir,—I have read with interest the report by Dr Carse and his colleagues on the Worthing experiment for a similar service has been in existence in most parts of the Manchester region for several years and its value is well recognised

In Bolton, for instance, a small psychiatric unit at a general hospital provides diagnostic and treatment clinics, day-hospital facilities, domiciliary service, and a psychiatric social club run jointly with the medical officer of health

Under present legislation, however, the success of a district service must depend on the cooperation of the local health authority and the support of the regional mental hospitals In Worthing the full cooperation of Graylingwell has apparently been enlisted, but it would be of interest to know how the public-health services have fitted into the scheme and what part the D A O s play The high degree of screening before admission to Graylingwell is certainly impressive

In some areas of our region it is felt that unless the local authority can provide more welfare and hostel accommodation the work of district mental health service will be hindered It is also important that a clear division should exist between the functions of a local psychiatric service and that of a large mental hospital With early outpatient treatment mental hospital beds will be needed mainly for the more severely disturbed and long-standing patients, many of them aged, and some hospitals—overcrowded as they are—may be reluctant to accept these "less promising" patients On the other hand, our experience shows that if a local service is accepted by the community, many patients are less willing to enter large mental hospitals

Finally, a clear system of priorities should be drawn up Once the facilities are available there is a constant increasing demand for the service, and the treatment centre may soon turn into a disposal centre for the increasing number of geriatric, "chronic sick" patients, not to mention additional work, brought by such agencies as the courts, probation service, and children's officers Unless the service is as well staffed as Worthing's seems to be, delays and disappointments will be inevitable

Royal Infirmary, Bolton

J T Leyberg

ANTIBIOTIC PROPHYLAXIS

Sir,—In reference to your valuable annotation (Jan 4), I should like to express my full agreement with your conclusion that antibiotics should not be used to prevent sepsis One risk is that of sensitisation This occasionally follows the prophylactic use of penicillin The result is disastrous if the antibiotic has, at any time later, to be used to combat actual sepsis

When arthritis is caused or aggravated by focal sepsis, the eradication of the focus may be essential to cure Here prophylaxis of some kind is necessary to prevent what otherwise might be a severe reaction Over many years I have never found prophylaxis with one of the sulphonamides to fail I have always prescribed sulphathiazole 1 g 4-hourly for 24 hours before and 48 hours after the operation Now that long-acting sulphonamides are available, 1 g daily for the same period has so far worked equally well

London, W 1

H Warren Crowe

COMBINED BARIUM MEAL AND CHOLECYSTOGRAPHY

Sir,—Dr Robinson [1] evidently does not favour any technical variation which might interfere with the accuracy of cholecystography, but perhaps he expects too much from this examination There are claims that cholecystography is 96–98% accurate The confirmation of the radiological findings is based on surgery, which by inference must limit the criteria for pathology to non-function or the presence of gallstones Where cholecystography fails is in chronic cholecystitis in a gallbladder which still retains some function It might seem possible to assess function according to the density of the shadow, but there are so many factors—physiological and physical—which influence contrast that such an examination would be almost valueless When the demands of a large general hospital can be eased by a combination of examinations it is reasonable to adopt this technique, and we cannot agree with Dr Robinson that the fine detail of the examination is sacrificed Indeed we have made some striking films of small calculi

In reply to Mr Forty,[2] we certainly agree that calculi may exist without producing symptoms, but this also applies to a non-functioning gallbladder It is in these patients that the combined technique is so useful in bringing to light associated lesions in the gastrointestinal tract which may account for some of the 30% of postoperative failures discussed by Ogilvie

In a recent series of 2000 patients examined by this combined technique, 193 (9 7%) had pathological gallbladders 100 of ese showed no evidence of function, and 93 functioned but ontained opaque or non-opaque calculi

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[1] Robinson, M I *Lancet*, 1957, ii, 1170
[2] Forty, F *ibid* p 1339

	Functioning with calculi	No function
ormal barium series	54	61
uodenal ulceration	6	6
astric ulcer	2	4
adiological evidence of gastritis	0	1
iatus hernia	11	10
arcinoma of stomach	1	0
uodenal diverticula	4	5
revious gastrointestinal operations	9	5
wo or more of the above lesions	3	4
iscellaneous	3	4

In a total of 193 pathological gallbladders, 78 had an associ- ted lesion in the upper alimentary tract

A S JOHNSTONE
M D SUMERLING

Department of Radiodiagnosis,
University of Leeds

MANIPULATION FOR BACKACHE

SIR,—As Mr Bremner (Jan 4) infers, a great deal of onsense is talked about manipulation It is therefore a ity that his painstaking work is invalidated by the com- lete absence of control cases in his series When dealing ith something as personal as low-back pain it is impos- ible to eschew patients' subjective impressions, but I ind it difficult to believe that so few of his cases exhibited bnormal physical signs Thus instead of a useful tatistical stick with which pro- or anti-manipulation xtremists might have been beaten, we are left with just ne more straw composed of clinical impressions

One must also deprecate Mr Bremner's failure accurately to define on *clinical* grounds what is meant by "lumbosacral strain" Even when accompanied by a half-hearted apology, usage is no excuse for the use of such a term which, though certainly "concise", is meaningless as he himself demonstrates This does nothing to further the introduction of order into the chaos of dogma and empiricism which surrounds the subject of backache and its treatment

Finally, it should not prove very difficult to explain the incidence of backache in the ratio of 1 8 females to 1 male in Mr Bremner's series A careful analysis of how the average day is spent would probably show that most of the 116 married women were subjected to more "externally applied strain" than most of the 84 males The average modern housewife does not apply many sudden, violent, and dramatic strains to her back, but the sum of the stresses imposed by household chores, children, and not infrequently a whole- or part-time job as well, is immense, as can be testified by any husband who has tried to cope alone for a few days

St Thomas Hospital,
London, S E 1

D R L NEWTON

SIR,—Being "osteopathically" inclined, and seeing many patients with backache, I was interested and pleased to read Mr Bremner's article (Jan 4) I should like to point out that we osteopathically inclined have never claimed a 100% cure-rate, but we do claim a high proportion of good results I was particularly pleased to see such good results even with non-specific "orthopædic" manipulation

If we use greater care in diagnosis instead of grouping all patients together under this vague heading of "lumbosacral strain", and if specific treatment is given to each type of low backache, then the results should be still better than those quoted by Mr Bremner This is in fact so

If we lumped together all patients with indigestion and treated them with alkaline powders, there would be some good results, but if they were analysed carefully and treatment prescribed accordingly, there would certainly be a higher percentage of good results

Differential diagnosis of low backache is difficult, but it is a mistake to say that "physical signs are few or absent" The points to look for are the mobility range of both the area and the individual joints, the tenderness in interspinous ligaments, the tension in the erector spinæ muscles, the relative position of one vertebra to the next, the kyphoses, lordoses, and scolioses, and finally changes in the erect radiographs and mobility films

The first and fundamental differential point is to distinguish between hypermobility and hypomobility To manipulate joints which are already hypermobile is likely to give bad results The differentiation can be made by palpation and mobility radiographs

If there is hypomobility but no lesion or root signs, manipulation is almost always indicated The next point is to locate the site of restriction so that the manipulation can be applied to the faulty joint rather than to the whole lumbar spine It is better, and easier, to achieve a specific manipulation without an anæsthetic than with one

If hypermobility is found, a corset and strengthening exercises are indicated, or injections of sclerosing fluid into the interspinous ligaments [1]

Mr Bremner found that in 3 6% of patients the condition was aggravated by manipulation These, and some of those not improved, probably had the hypermobility type of low backache where the ligaments are overstretched already I realise that his series aimed specifically at determining the benefit or otherwise of one manipulation, and to that end the experiment is to be commended But if in private practice one were to make 3 6% of one's patients worse, it would soon ruin the practice A bad reputation travels faster than a good reputation

London, W 1

ALAN STODDARD

SEX REVERSAL

SIR,—Dr Ashley and Dr Jones (Jan 11) are to be congratulated on their critical discussion, which helps to clarify the position of their lucidly presented case in the increasing complexity of intersex states I have recently seen three unusual examples of gonadal dysgenesis, all with male nuclear sex

The first patient, an otherwise classical example of Turner's syndrome with short stature and webbing of the neck, has apparently menstruated for seven years, the second is a colour-blind dwarf whose father has normal colour-vision, and the third is a tall eunuchoid female with no stigmata of Turner's syndrome The third case, similar to those reported by Swyer,[2] and different from that of Ashley and Jones in that the leucocytes show typical male morphology, is probably a variant of gonadal dysgenesis,[3 4] and helps to stress that reclassification is required

You rightly say, Sir, that there is urgent need for a new terminology, and though your discussion is mainly concerned with examples of sex reversal, it is very important that any classification must also include cases of chromatin-positive Turner's syndrome and of chromatin-negative Klinefelter's syndrome At the symposium on nuclear sex, a committee was appointed to consider the question of nomenclature, but your plea of urgency suggests that the matter might now be discussed profitably in your columns

In the many types of pseudohermaphroditism, which include testicular feminisation and congenital adrenal virilism, gonadal sex and nuclear sex are in conformity and the defect is apparently not primarily due to dysgenetic gonadal development. In other intersex states, however, gonadal involvement does appear to be of primary importance and the corticomedullary balance theory of gonadal differentiation seems to be a suitable basis for classification and nomenclature Such a scheme, which can be conveniently tabulated and is self-explanatory, is offered below for comment Some of the least ambiguous of the old names, shown in parentheses, might continue to be used, but a name is required for the case recorded by Ashley and Jones, and a new name for the Klinefelter syndrome and its modifications is long overdue

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[1] Hackett G S Joint Ligament Relaxation. Springfield, Ill., 1956
[2] Swyer G I M *Brit med. J* 1955 ii, 709
[3] Hoffenberg H Jackson W P U *ibid* 1957, i, 1251
[4] Swyer, G I M *ibid* p 1421

CLASSIFICATION AND NOMENCLATURE OF INTERSEX STATES

I Both Gonadal Components Dysgenetic
- (1) Underdevelopment
  - (*a*) Complete failure Corticomedullary agenesis (gonadal agenesis)
  - (*b*) Partial failure Hypoplastic corticomedullary dysgenesis (gonadal dysgenesis)
- (2) Overdevelopment of the component which should have been suppressed with collateral development of the other components Hyperplastic corticomedullary dysgenesis (true hermaphroditism)

II One Gonadal Component Dysgenetic (with non-development or suppression of the other component)
- A *Gonadal medulla dysgenetic*
  - 1 Overdevelopment Hyperplastic medullary dysgenesis (Chromatin-positive Klinefelter's syndrome)
  - 2 Underdevelopment Hypoplastic medullary dysgenesis (Chromatin-negative Klinefelter's syndrome)
- B *Gonadal cortex dysgenetic*
  - 1 Overdevelopment Hyperplastic cortical dysgenesis (case of Ashley and Jones)
  - 2 *Underdevelopment Hypoplastic cortical dysgenesis* (recognition awaited, but perhaps the case described by Hoffenberg et al[5] would fit)

Glasgow JOHN S S STEWART

GALLSTONES AND THE SURGEON

SIR,—In your leading article of Dec 21 no mention is made of intraoperative cholangiography The indications for exploration of the common duct given by Ogilvie[6] are rather vague, and in fact they may be misleading In the majority of cases intraoperative cholangiography reveals unequivocally the presence of stones or papillitis

Department of Surgery,
University Hospital,
Basle, Switzerland RUDOLF NISSEN

A THYROID ASSOCIATION

SIR,—The suggestion from Professor Fraser and his colleagues (Jan 11) for forming a Thyroid Association of Great Britain deserves the very strong and full support of all those interested in thyroid disease

Such an association could be greatly strengthened by extending membership to Ireland and the Commonwealth, where valuable scientific contributions are continually being made

A similar association in Europe would then work in close harmony with this body and the well-established American Goiter Association and their related endocrine societies

Regional advance in the understanding of thyroid and allied diseases could be stimulated and canalised by each of these bodies and periodically coordinated by more frequent international meetings

No international goitre meeting has been held previously in Great Britain The last such gathering took place in Washington in 1938 With to-day's easy and rapid air travel, these long intervals seem out of date in such a swiftly advancing field of research

As I said in your columns[7] and elsewhere[8] in advocating an international meeting on thyroid nomenclature, much potentially valuable work is being invalidated by uncoordinated methods of investigation and procedure This is particularly so where advances in thyroid research have recently invaded so many fields and disciplines

The flourishing American Goiter Association, at whose meetings we have been made most welcome, is an example of the great good such a body can achieve The invaluable active support of the Royal Colleges of Surgeons and Physicians would also give a strong impetus to the creation and growth of a similar organisation in our midst

London, W 1 T LEVITT

RADIATION AND LEUKÆMIA

SIR,—The data reported in our study of leukæmia in patients irradiated for ankylosing spondylitis (to which Dr Pochin refers in his letter of Jan 4) were collected at the request of the Medical Research Council, in the hope that they would provide some indication of the nature of the relationship between the dose of radiation and the resulting incidence of the disease Although it was realised that no direct information would be obtained about the effect of doses as low as those commonly given in diagnostic radiology, it was hoped that it might be possible to estimate their effect by extrapolation from the results at higher levels of dose It transpired, however, that quite a large number of patients were given radiation to areas other than the spine and sacroiliac joints, and for these patients it proved impracticable to estimate the size of the relevant dose (assumed to be the mean dose to the active bone-marrow) Our principal analysis was, therefore, limited to the group of patients whose treatment was directed solely to the spinal axis and for whom we obtained reasonably accurate data on the distribution of radiation dose within the spinal marrow

In this group 18 patients developed leukæmia The mean spinal-marrow dose received by these patients varied between 315r and 2195r, and it is clear that the data could not provide firm evidence of the quantitative effects at really low levels of dose On the other hand, the data gave no positive indication of the existence of a threshold below which no effect was produced, and the incidence of leukæmia observed in the general population (presumed to have had no therapeutic dose) was close to that estimated for zero dose from the observed incidence at other levels We therefore suggested, as a working hypothesis, that there was no threshold dose for the induction of the disease and included the point representing the estimated incidence for zero dose in the data from which the quantitative relationship between dose and incidence was calculated

If (as Dr Pochin suggests) the point for zero dose is omitted, and a regression line calculated from the incidence-rates for spondylitic patients alone (standardised for age and weighted according to their reliability) we obtain the equation $y=0\ 00634x-0\ 34$, where y is the annual incidence per 10,000 men at risk, and x is the mean spiral-marrow dose in röntgens Hence the estimate of therapeutic dose which would correspond to zero incidence is 54r

In view of the paucity of data the error of this estimate is liable to be very large If the probable limits of the regression line are calculated by a method similar to that derived by Irwin,[1] it is found that the 95% confidence limits for the "true value" of the dose corresponding to zero incidence are −1700r and +400r In other words, the threshold value may be zero or anywhere between zero and 400r This calculation is made on the assumption that all the cases of leukæmia in the treated series were due to irradiation If, however, some of the cases were due to other causes, the estimate of the probable threshold dose would be slightly higher If no case of leukæmia occurring in the general population was due to irradiation, the estimated threshold dose would correspond to an incidence in a sample of the general population of the same age-distribution as that in the population of spondylitics (i e , 0 49 cases annually per 10,000 men) and would be about 130r therapeutic dose with a likely upper limit of about 460r

All these doses, it must be stressed, are mean doses to the spinal marrow If it is assumed that there is a linear relationship between dose and incidence and that there is no threshold for the induction of the disease, it is possible to convert a mean spinal dose into a mean dose to the whole active marrow In our report this was done by dividing by a factor of 2 to 3, since it was thought that the spinal marrow constituted between a half and a third of the total active marrow If, however, it is postulated that a threshold exists, such a conversion is impossible, in this case, there is no real justification for using a mean spinal dose as the measure of effective dose in the study of the dose/response relationship, and it might be thought preferable to relate the incidence of leukæmia to the maximum dose received at a point in the marrow Such an analysis was made during the course of our investigations, and the results were reported in Appendix B of the Medical Research Council's report on *The Hazards to Man of Nuclear and Allied Radiations* This analysis also provided estimates of incidence which appeared to be proportional to the dose and certainly gave no indication of the existence of a threshold For reasons which are discussed in our report, however, we felt that this method of analysis might introduce a systematic bias into the results, and we preferred to use the mean spinal marrow dose as the best estimate of the effective dose

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[5] Hoffenberg, H , Jackson, W P U , Muller, W H *J clin Endocrin* 1957, 17, 902
[6] Ogilvie, W H *Ann R Coll Surg Engl* 1957, 21, 319
[7] Levitt, T *Lancet*, 1957, ii, 1065
[8] Levitt, T *Postgrad med J* 1957, 33, 352

[1] Irwin, J O *J Hyg , Camb* 1943, 43, 121

In conclusion it is clear that we continue to be ignorant of whether or not a threshold dose exists One way in which the problem may be solved is by undertaking further epidemiological studies, comparable to the survey of irradiated cases of ankylosing spondylitis To plan such surveys, however, it is necessary to proceed on the basis of some hypothesis The data obtained in our study led us to the conclusion that the most reasonable hypothesis to work with was that no threshold existed and we see no reason to modify it We hope that no-one will mistake the delineation of a working hypothesis for a statement of established fact

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W M COURT BROWN
RICHARD DOLL

A THEORY OF NERVE DEAFNESS

SIR,—The hypothesis of Mr Gregory and Miss Wallace (Jan 11) concerning causes of impairment of hearing in what they call " nerve " deafness is interesting, but it seems to me that they formulated this view with only limited background information about the various types of non-conductive impairment of hearing

They mention that the terminology of non-conductive deafness is confusing, but surprisingly they themselves made a mistake leading to further confusion They call an impairment involving predominantly high frequencies " presbyacusia " This is, however, a term used for one definite type of deafness, clinically well known—that is, old-age deafness Old-age deafness has some distinct peculiarities, and therefore to call all types of high-note impairment by this term is confusing Moreover, they call this type of " nerve " deafness, characterised by a predominantly high-note loss, the typical one, and imply that it is numerically the most important, allowing certain generalisations This is incorrect There are several types of deafness (not conductive) which do not have this " typical " predominantly high-frequency loss Even in Ménière's disease, in the more developed cases, the audiogram is more often " flat "—that is, showing a more or less uniform loss for all frequencies Another type of non-conductive deafness in which the lesion is also in the end-organ (that is, deafness from maternal rubella) has also this characteristic " flat " audiogram without a predominantly high-note loss There are some indications of recruitment also in these cases of deafness from maternal rubella

Further, there are types of hearing loss, undoubtedly non-conductive, in which not only is there no predominantly high-note loss, but the hearing is distinctly *better* for the high notes We are at present studying these types, and I have not only numerous audiometric records available but also *histological* evidence that the lesion is undoubtedly in the end organ—namely, in the organ of Corti

In all these cases, of course, there is a considerable reduction in channel capacity of the communication system, caused by some disturbance in the end-organ, but no reduction of high-note discrimination as a result of it This is against the suggestion of Mr Gregory and Miss Wallace that reduction in channel capacity by an end-organ lesion leads to an impairment of high-frequency discrimination

I must also mention that not only is there often a tendency in " nerve " deafness for an inner-ear lesion to produce a uniform loss for all frequencies but also a typical predominantly high-frequency type of deafness is often caused by a lesion which is *not* in the end-organ but higher up in the auditory pathway A good example is deafness from hæmolytic disease of the newborn We are studying another type in which there is also a symmetrical loss predominantly for the higher frequencies, and in which we have good reasons to believe that the location of the damage is not in the end-organ but at certain levels in the auditory pathway We hope, to report these findings soon, and also to give a theoretical explanation why the high frequencies are affected

I am not saying this to dispute the possibility that, in some cases, random neural noise, affecting unfavourably the noise-to-signal ratio, may not impair discrimination in the high-frequency range, but when a general hypothesis is formulated at this early stage of study, it is dangerous to disregard certain factors which contradict it from the beginning This may lead to a false theory

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L FISCH

LABORATORY DIAGNOSIS OF CONGENITAL GALACTOSÆMIA AT BIRTH

SIR,—In the article by Dr Schwarz and his colleagues describing the laboratory diagnosis of congenital galactosæmia at birth (Jan 4), reference is made to a milk-free diet described by Holzel in 1954 [1] In his original article Holzel states this diet to be " a modification of Moll's pudding, consisting of Farex, eggs and sugar in appropriate dilutions "

May I draw your attention to the fact that the present preparation of ' Farex ' (Glaxo) contains separated milk powder ? This has been added to the product since September, 1954, so that farex now contains 5% separated milk powder and 2 5% lactose In view of the varying tolerance to lactose exhibited in those cases of galactosæmia reported in the literature, it seems advisable that those who may need to use farex should be made aware of its present composition

St. Bartholomew's Hospital,
London, E C 1

MARY FURNIVALL
Chief Dietitian

PREGNANCY AND COARCTATION OF THE AORTA

SIR,—I have read with interest the article by Dr Goodwin (Jan 4) on the risks of pregnancy in coarctation of the aorta, in which he analyses 13 cases of his own and 123 cases previously published He concludes that the hazards of pregnancy in unrelieved coarctation depend largely on the presence or absence of added cardiovascular lesions, especially those of the aortic valve As prophylactic resection of the coarctation is being increasingly performed in young persons, the prognosis of coarctation treated conservatively will become harder to assess I wish therefore to report a case seen in general practice

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[1] Holzel, A *Med ill* 1954, 8, 44

A woman, aged 37, has coarctation and pulmonary tuberculosis When she was 19, she was referred to a tuberculosis officer for his opinion, and coarctation was first diagnosed by the radiologist from the well-marked notches on the ribs Full assessment at that time showed no hypertension (blood-pressure in arms 130/80 mm Hg), and no evidence of aortic incompetence or other cardiac lesion The electrocardiogram was normal Subsequently she married, and had four normal pregnancies terminating in one forceps and three normal deliveries Her last pregnancy was at the age of 35, and she was sterilised during the puerperium. Although her blood-pressure has been labile, she did not develop hypertension during any of her pregnancies, and only during the past year has her blood-pressure started to rise Her coarctation remains remarkably symptom-free, and she leads the full life of a busy housewife She has moderate dyspnœa on exertion, which is largely a sequel of pulmonary tuberculosis

This patient's history confirms the fact that careful conservative management of four pregnancies may be undertaken without deleterious effect when coarctation is uncomplicated by additional cardiac disease

Bungay, Suffolk W M JORDAN

A FUNCTIONAL NECESSITY

SIR,—I was much interested by Professor Platt's letter[1] on the subject of consultant appointments, and I heartily agree with him that it would be wrong to create a new subconsultant grade However, a prerequisite to proper staffing is a knowledge of the needs of the individual regions, and such knowledge seems peculiarly hard to acquire

When I was a member of the North West Metropolitan Regional Hospital Board's medical committee, it took me some months to get the officials even to allow a discussion on this subject When we asked for the report of the Ministry of Health working party which had reviewed the consultant establishments of the region, we were informed that their report had never been published In September of last year I once again endeavoured to ventilate this subject in the medical committee of the board A request for details of the existing consultant and S H M O establishment in the region, and for information about all requests for additional consultant appointments, was met with the written reply

> "The information requested would be most difficult to assemble and would involve a close examination of all the Board's records on medical staffing since 1948 Quite apart from this the Board's staff is so sorely pressed at the present time that to embark on this project would be quite impossible "

When regional-board officials and others show such scant interest in a problem of major importance, and when serious impediments are placed in the way of medical committee members who endeavour to secure factual information, it would seem high time for the Joint Consultants Committee to urge a nation-wide review of consultant establishments I would further suggest that the various regional consultant and specialist committees should press their respective regional boards so as to ensure that the necessary information is made available Once our professional committees have the facts it may be easier to overcome the deadly inertia and official buck-passing of the present time

Radlett, Herts REGINALD S MURLEY

SIR,—The logic of Mr Brearley's letter of Jan 4 is incontestible The solution to the senior-registrar problem now and in the future lies in the appointment of more consultants, especially in general medicine and general surgery However, the Ministry are unlikely to make any movements in this direction without being convinced that the hospital consultant service is in imminent danger of breakdown Unfortunately, the undoubted shortage of consultants has been obscured since the inception of the service by the fact that most consultants have been working overtime This habit, which would be condemned immediately by any trade union, seems to be inseparable from a vocational profession Ironically enough, the Minister is already supplying the remedy in the form of economic pressure, resulting from the steady decrease in the real income of hospital employees No longer will these doctors be able to subsidise the health service on the scale which has applied in the past They will be too busy attending to the chores, the repairs, and the decorations at home where adequate help can no longer be afforded Waiting-lists will grow and the problems in question will be solved much more quickly than they would ever be as a result of the negotiations which are *proceeding interminably*

Liverpool NORMAN GIBBON

SYRINGES CLEAN OR STERILE?

SIR,—Your annotation of Jan 4, drawing attention to the Nuffield Provincial Hospital Trust's book on the planning and organisation of central syringe-sterilisation services, is most welcome, and I hope will further accelerate the spread of such services throughout our hospitals In terms of economy and preventive medicine, central syringe sterilisation should appeal to lay and medical members of boards of management alike

It seems timely, too, to consider sterilisation of syringes in public health clinics and general practice, especially on account of the impending inoculation of adults against poliomyelitis

Mass inoculation campaigns in children, using one syringe, and a different, recently sterilised, needle for each child, have been happily free from the spread of syringe-transmitted hepatitis In adults, however, such substandard technique—excused by some on grounds of practicability—seems likely, in the light of experience, to prove dangerous There is ample proof in the literature that irrespective, of the type of injection, epidemics of hepatitis are likely to occur in clinic populations where *each patient is not served with a sterile* syringe and needle Hepatitis is not generally listed by public health authorities as a notifiable disease, and since its incubation period is long, much harm may be done before the dangers are fully appreciated

Public health authorities and general practitioners, no less, therefore, than hospitals, would do well to reconsider their sterilisation arrangements, not only in terms of preventive medicine, but also perhaps, since the consequences of using contaminated equipment are well established, from the medicolegal aspect also

Stockport R S MORTON

SIR,—Your annotation of Jan 4 makes no mention of the problems of syringe sterilisation in general practice

I have obtained a supply of 2 ml Luer lock syringes wit number-17 hypodermic needles mounted and protected by metal needle guard These are packed in a cylindric screw-capped metal container, with a small cotton-wo plug

The containers are autoclaved for me at my local hosp and I imagine that most hospitals would cooperate w family doctors in this way

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[1] *Lancet*, 1957, ii, 1336

A safe sterile syringe in one's coat pocket car or visiting bag, ready for immediate use, with a sterile plug of cotton-wool for skin preparation, is particularly useful when answering an emergency call

London, S.E.26. R N JACKSON

TUBERCULOSIS IN THE SCHOOL

SIR,—Many will agree with the opening and closing sentiments of your annotation [1] Certainly the tuberculin test is a very useful tool in investigating the epidemiology of tuberculosis among schoolchildren. Not only does a positive reaction indicate which children need to be examined more carefully and followed, but the identification of those who have been in contact with an infectious case of tuberculosis makes it possible to identify the source case among their current associates Moss and Fairweather [2] have again demonstrated the great value of this approach to the prevention of tuberculosis

At the same time, the Clitheroe experience clearly points up a serious disadvantage of B C G vaccination Aside from the question of the logic of vaccinating the children who were still uninfected after the source cases had been removed, the positive tuberculin reactions engendered by B C G will make a similar surveillance impossible in the future Is not B C.G vaccination under these circumstances rather like killing the goose that laid the golden eggs?

Tuberculosis Program,
Division of Special Health Services,
Public Health Service,
Washington 25, D C.

GEORGE W COMSTOCK

HÆMORRHAGE IN LIVER DISEASE TREATMENT WITH SEROTONIN

SIR,—We have had the opportunity of testing serotonin in three cases of hæmorrhage appearing in the course of severe liver disease

One patient had juvenile cirrhosis (postmalarial?) with hypersplenism (leucopenia, thrombocytopenia), hæmorrhages and purpura, treated by splenectomy, two had severe and protracted epidemic hepatitis (post-transfusional in one) with a severe hæmorrhagic state characterised by spontaneous ecchymosis

To estimate the efficiency of serotonin the following tests were carried out before and after the beginning of the treatment with serotonin

The bleeding-time, the coagulation-time of the venous blood at 37°C (Lee-White), the Rumpel-Leede test after venous stasis at over-diastolic arterial pressure for 5 min, the clot retraction (serum expressed per 5 ml blood after 60 minutes in the incubator), and the platelet-count.

Serotonin 1–2 vials of 5 mg intramuscularly, was given daily for a few days. It was well tolerated and produced no local or general reactions such as were seen after intravenous administration (e.g, tachycardia, hypertension and dyspnœa) Improvement in the hæmorrhagic state was indicated by cessation of bleeding in the skin and alimentary-tract hæmorrhages The bleeding-time diminished in all three cases (see table) The coagulation-time improved the Rumpel-Leede sign became negative, and the clot retraction improved, but the number of platelets remained at the same low level

From our data it seems that serotonin acts especially on the capillary resistance and clot-retraction without influencing, in the doses used, the number of platelets.

The serotonin was kindly supplied by Messrs Hoffmann-La Roche

Hospital of Infectious Diseases,
Colentina Bucharest, Rumania.

NEUMAN MAYR
P TEODORESCU

EFFECT OF SEROTONIN ON HÆMORRHAGIC STATE

Patient	—	Bleeding-time	Coagulation time	Prothrombin time (Quick) (sec.)	Clot retraction (ml serum)	Platelets (per c mm)	Rumpel-Leede test
1	before	4 min. 15 sec.	9 min	16 (control 12)	1·1	76,000	++
	after	2 min. 30 sec 2 min 50 sec.	5 min 30 sec 5 min. 10 sec.	15	1·8	72 000 68,000 66,000	±
2	before	3 min 10 sec.	8 min 10 sec	18 (control 13)	1·2	54,000	++
	after	2 min 30 sec 2 min 40 sec.	4 min 50 sec. 5 min 10 sec	17 16	1·9	46 000 38,000 52,000	+
3	before	3 min 40 sec	9 min 50 sec. 5 min 50 sec.	24 (control 14)	1·0	38 000	+++
	after	3 min 10 sec 2 min 20 sec	5 min 40 sec	23 22	2·4	46 000 42,000 48,000	±

THE DIFFICULT KNEE

SIR,—May I congratulate you on your annotation of Dec 14[3] I should however, like to discuss several points

(1) A knowledge of the mechanism of injury is essential.

(*a*) A direct injury can cause contusion and bruising of the soft-tissue structures such as the infrapatellar pad of fat, alar folds, synovial membranes, and menisci as well as the articular cartilages and bones of the tibia, femur, and patella Unless these cases are treated by immediate active methods, including rest from all forms of strain, and appropriate graduated exercises, complications tend to develop which include an unstable knee, a stiff knee, articular cartilage erosion, chondromalacia patellæ, and early joint degeneration It would seem that too many cases with a history of direct injury are subjected to menisectomy far too soon The effects of contusion and bruising, if allowed to become chronic, may take many months of treatment to overcome especially if the case has been neglected at the beginning

(*b*) The components of an indirect injury must be clarified Was it a purely abduction strain or was there an element of rotation and flexion as well? A hyperextension injury may contuse the infrapatellar pad of fat and involve the structures in relation to the tibial spine as well as stretching or tearing the posterior capsular structures It should be realised that in an indirect injury the structures on one side of the joint are stretched or torn, whereas those on the opposite side may suffer direct injury and be contused and bruised

(2) Before operation the stability of the joint must be assessed One of the menisci may be torn, but the prognosis is entirely different when there is a stable knee and when there is cruciate or lateral ligament laxity The knee may give way on occasions without true locking and McMurray's tests may be negative, but often, although flexion may appear to be full, a rubbery elastic feeling can be elicited and there is a distinct difference in the feel of the two sides The patient

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[1] *Lancet*, 1957, ii, 784
[2] Moss, P S., Fairweather, J H *Brit J Tuberc* 1957, 51, 258

appreciates this difference as he can do a full-knees bend on the good side but not on the affected one

(3) At operation the femoral and tibial articular cartilages must be observed and the patellar one as well if necessary These findings are important in regulating the tempo of convalescence and rehabilitation The stability of the ligaments is again assessed under anaesthesia and direct vision A recent case illustrates this point

A young rugger player aged 17 showed signs of a torn medial meniscus of the right knee At operation there was no evidence of articular-cartilage damage and the ligaments were normal He made a quick convalescence and had no trouble with this knee Three years later he injured his left knee while parachuting and the knee continued to give way on several occasions At operation, apart from the tear of the medial meniscus there was evidence of early erosion of the articular cartilage on the medial condyle This knee now is returning to full function slowly

In a case of this sort it is essential not to force strenuous activity

(4) Chondromalacia patellæ is certainly a common sequel to any injury of the knee-joint, but it often occurs in childhood and adolescence from no apparent cause These cases can often be kept in circulation by modifying one of their activities such as avoiding P T and Corps work at school but allowing cricket and even football They should wear sponge-rubber heels to avoid jarring and carry out conscientious daily home treatment and physiotherapy, first as a course and later once a week Without treatment the condition progresses and may require operation Occasionally, in spite of great care operation may be inevitable

(5) Every case of injury to the knee-joint, especially a joint in which menisectomy has been performed, is a potential case of osteoarthritis The early physical signs of this condition are articular cartilage rolling and synovial thickening Sometimes in these latter cases even radiographs show a normal joint, but this constitutes the pre-X-ray phase of osteoarthritis and is reversible with appropriate treatment Removal of a meniscus may be necessary in a middle-aged man associated with early osteoarthritis but it must be remembered that the operation itself gives three weeks' rest from strain and in the more advanced osteoarthritis simple removal of the meniscus does not make them symptom-free The patient is warned of the likelihood of osteoarthritis and if he will only persist with regular home treatment indefinitely he can delay the onset This claim will be open to criticism but many patients in whom osteoarthritis has developed have been helped by home treatment and courses of physiotherapy and lose their physical signs and symptoms If a claim for a cure for osteoarthritis had been made 20 years ago the doctor would be considered a charlatan, but since it has been proved that articular cartilage can regenerate patients showing early osteoarthritis can themselves become symptom-free It is essential in these cases, however, for the patient to continue home treatment indefinitely

(7) In about 2–5% of cases in which the diagnosis is difficult and in doubt, I have always found that arthrograms, as carried out by Somerville, have supplied the answer in almost every case As performed by him this is a method without danger

(8) Few textbooks draw attention to the secondary effects on the joint above and below the injury Such muscles as the hamstring and adductor magnus affect the movements of the hip as well as the knee, and in knee injuries they tend to contract and shorten This also applies to the calf muscles and their effect on the movements of the ankle-joint Full extensibility and flexibility of the muscles must be restored with full movements of both ankle and hip as well as the knee before the patient can expect to have a knee which is 100% No patient with a knee injury should be labelled "functional" until full movement has been obtained in the hip, knee, and ankle joints as well as restoration of full muscle power To obtain this the knee may have to be subjected to a series of controlled manipulations under thiopentone, as well as long courses of physiotherapy including gentle manipulations

London, W 1 **W E Tucker**

ENZYME TESTS FOR GLUCOSE

Sir,—May I support Dr Miller's view (Jan 11) of the reliability of the enzyme tests ('Clinistix' and 'Testape') as a means of detecting, but not measuring, urine-glucose?

The 11% of discrepancies found by Tunbridge et al,[1] and quoted in *Prescribers' Notes* (May, 1957), arises from the assumption that a negative reaction with 'Clinitest', or other copper-reduction tests, means that glucose is absent, whereas the true position is that the enzyme tests can detect a lower level of glycosuria than can clinitest, though the clinical significance of such a trace of glucose may be slight

Reducing sugars other than glucose are not, of course, detected by the enzyme tests, but I have encountered only two substances which give false-positive reactions—namely, hydrogen peroxide and hypochlorites The first is largely of theoretical interest, but many household and laboratory cleansers contain hypochlorites, and false positive reactions can arise from gross contamination of urine containers

I should be very interested to hear of a positive reaction in uncontaminated urine, where glucose was proved to be absent —e g, by paper chromatography

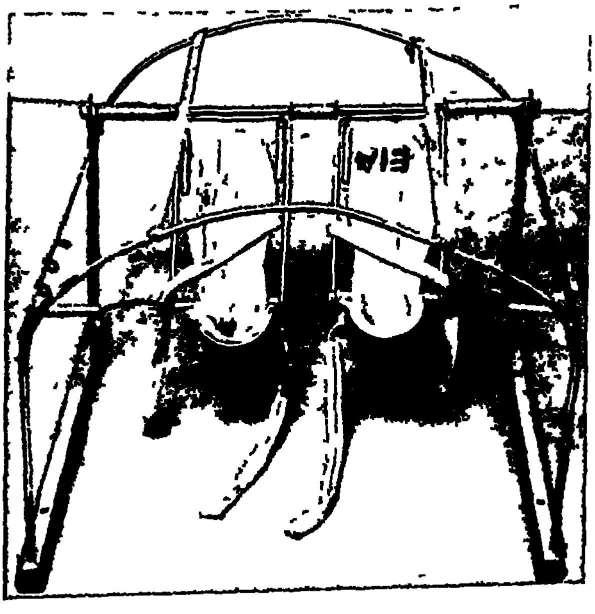
The specificity of glucose oxidase is not in dispute, and false-positive reactions are more likely to arise from substances capable of oxidising *o*-tolidine to give the blue pigment So far as I am aware, no such substance has been found in urine

Department of Clinical Chemistry,
Royal Infirmary, Edinburgh
Samuel C Frazer

POSTOPERATIVE VENOUS THROMBOSIS

Sir,—Your leader of Nov 30 and Dr Rivlin's letter (Dec 21) draw attention to the need for active movement in the lower limbs in the prevention of venous thrombosis in recumbent patients, and as a necessary supplement to anticoagulants in the treatment of established venous thrombosis

Many patients, however, are in need of exercise, but unfit to get up Encouragement to move about in the bed, or to keep the lower limbs moving, is often insufficient to ensure adequate venous return, and many are naturally apprehensive lest they injure themselves or their operation wounds There are special



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[1] Tunbridge, R E, Paley, R G, Coulson, D *Brit med J* 1956, ii, 588

indications for actively exercising the legs in thrombophlebitis, and where venous thrombosis is feared after operation or during long recumbency For this reason a leg exerciser was devised, the objects of which were

To allow movement against resistance, both at the ankles and knees, which the patient could continue to perform as required and without undue fatigue.

To provide suitably padded pedals without danger of damage from friction or pressure over the skin of the heels or elsewhere.

To make the apparatus portable and easily accommodated in a hospital bed beneath the bedclothes

The accompanying illustration shows the apparatus made for this purpose by the engineers' department at the Queen Elizabeth Hospital, Birmingham It was adapted from a standard bed-cradle, into which were built brackets to hold pedals suspended from above, hinged at suitable points, and attached to the cradle by springs, thus providing resistance to both ankle and knee movements Hooks were so fitted that the sites of attachment of the springs to the cradle itself could be changed, and their tension readily adjusted to suit the requirements of each patient.

This apparatus has proved acceptable to patients, comfortable in use, and of value in retaining muscle tone in recumbent patients It should be helpful in preventing postoperative and other thrombophlebitic complications, and, in conjunction with anticoagulants, accelerating the resolution of œdema of the legs in established cases of venous thrombosis

I am indebted to Mr T F Dee, clinical photographer at the Queen Elizabeth Hospital, Birmingham, for the illustration, and to the engineering departments of the Queen Elizabeth and General Hospitals, Birmingham, for making the apparatus

Edgbaston, Birmingham. G E OWEN WILLIAMS

SANATORIA BEDS

SIR,—In matters of medical treatment the pendulum of fashion is apt to swing too far and too fast Dr Beresford's letter (Jan. 4) is an example of this He can see no good in the larger sanatoria, where education of the patient, said by him to have little scientific basis, is still thought to be an essential part of treatment and rehabilitation Furthermore, such treatment is said to breed hypochondriacs Nothing could be further from the truth Considerable experience on both sides of the blanket has convinced me that the valetudinarian is a product of long domiciliary treatment The patient idling around at home loses a sense of purpose much more rapidly than the sanatorium inmate whose graduated activity is leading steadily on towards return to normal life and employment

Reading Dr Beresford's letter, one would think that the large sanatorium had nothing to offer except rules and regulations What about laboratory facilities, resident staff, and surgical units? It seems to me that many people have reached the erroneous conclusion that the treatment of pulmonary tuberculosis has become just too easy since the discovery of streptomycin—a conclusion which may be responsible for the increasing number of patients admitted to sanatoria harbouring resistant strains of the tubercle bacillus I have the good fortune to work in an area where adequate admission to hospital is still the treatment of choice in newly discovered cases, and as a result the proportion of resistant strains is below average It is still high enough to make the use of all three standard drugs advisable at least until the sensitivity of the strains are known 60% of our tuberculous admissions are still open cases

Presumably I am one of the "interested parties" who are striving to maintain the larger sanatoria But what of Dr Beresford? Are there also interested parties striving to maintain the smaller units?

Cheshire Joint Sanatorium,
Market Drayton, Salop A CLARK PENMAN

[illegible]

[illegible]

P.C., [illegible]

THOUGH [illegible] Ministers of [illegible] which he [illegible] background [illegible] politics Nevertheless [illegible] hall was firmly based [illegible] principles, and [illegible] health and [illegible] also a real [illegible] was at that time, [illegible]

He was born in [illegible] Lanark. From Glasgow [illegible]

Universal Pictorial Press

[illegible] recognised the value of [illegible] a contemporary recalls, "[illegible] but Elliot's arrows were [illegible] argument, he was a formidable [illegible] take with equal grace and [illegible] 1910 and M.B in 1913 he was [illegible] Royal Infirmary before he [illegible] 1914 to 1918 he served in France [illegible] Cross and bar

Almost immediately after [illegible] elected Unionist M P for Lanark [illegible] medicine began to slacken. For [illegible] public-health staff of a London [illegible] research on animal nutrition [illegible] (when John Boyd Orr was the [illegible] in 1923 But thenceforward the [illegible] in politics He held junior offices [illegible] ment, the Ministry of Health, and [illegible] ing the '20s In 1932 he became [illegible] in 1936 Secretary of State for Scotland [illegible] Minister of Health The quality of [illegible] bench and on the back benches of the House [illegible] are shown by these tributes from a Civil Servant and [illegible] a fellow M P

Elliot's stay as Minister of Health [illegible] left in 1940 when the plans for the [illegible] Services and evacuation were beginning [illegible] and when his experience and driving [illegible] enhanced his reputation as an administrator [illegible] of Health come and go, and Elliot bore his disappointment with equanimity

On visits of inspection in England and Wales he was a delightful companion, keenly interested in everything and enjoying temporary release from his desk He worked hard, too hard we thought sometimes, for he never spared himself He took a special interest in nutrition, fostered by his experience as Minister of Agriculture, and I recall many talks with him and Lord Boyd Orr New knowledge of the subject, partly through Elliot's influence, was embodied in the Government's rationing scheme

It is difficult to realise that he has gone from us That tall figure so full of vitality, enthusiasm, and brilliance, that fluent speech adorned with Scottish accent, wit, and humour, that desire to serve his country which led him to arduous missions abroad, and also to represent his Sovereign as Lord High Commissioner to the General Assembly of the Church of Scotland—all these seemed so essential a part of the national life

A S M

To most of us who were his contemporaries in Parliament, Walter Elliot will be remembered rather as an influential back-bencher than as a Minister and scarcely at all as a doctor "Colonel Elliot" frequently, "Mr Elliot" often, "Dr Elliot" hardly ever That he had an abiding interest in and affection for his first profession, medicine, there can be no question He served effectively as Under-Secretary for Health at the Scottish Office and as Minister of Health in Whitehall Yet he gave the impression that he was mindful of the saying current before his time in the Ministry that "doctors do not make good Ministers of Health" and preferred to base himself on a Parliamentary rather than a medical reputation He was not outstandingly active in the negotiations and debates over the National Health Service Bill But his position in recent years as a vigorous and respected back-bencher is unassailable and he was prominent in the discussions in the Conservative "1922 Committee" The niche he cut for himself was as an interpreter of back-bench opinion to Cabinet Ministers and as an interpreter of the Cabinet to the parliamentary party He could speak with freedom in both circles, knowing that his opinions would be listened to I can recall more than one occasion when tensions were resolved by his intervention at party meetings

His capacity for friendship, his wise and well-stored mind, and his exceptional experience meant that he was often called to head delegations and to speak as a representative parliamentarian This was a role in which he seemed more at home than in the rough and tumble of party politics—though he never disdained the dust and turmoil of party conflict—and will be the contribution to the work of the House of Commons for which he will be gratefully remembered by those who worked with him The House needs a handful of statesmen free to move at need above the arena of our daily concerns Walter Elliot, by his natural endowments, his personality, and his experience was one of these The House has too few of them and his death is a real loss **H L**

Though Elliot did not return to Ministerial office after 1940, as these tributes show he continued to give much valuable service One of his interests in these last years linked him once more directly to medicine, and of his presidency of the Royal Institute of Public Health and Hygiene J B A, who had known him since they were both students in Glasgow, writes

Immediately after the first world war I, then an R M O at the Royal Chest Hospital of London, renewed my acquaintance with Walter Elliot who, though his foot was on the first rung of the political ladder, was at that time interesting himself in public health and acting as a part-time assistant to a medical officer of health in a London borough We had many conversations over lunch at the hospital and I was impressed with the keen interest which he took in preventive medicine Later it was my privilege as a member of council of the institute to approach Elliot to ascertain whether he would be willing to become our president It was characteristic of the man that he did not accept this office before acquainting himself with the work and activities of the institute From his election in 1946 he was not only a figurehead but an active president, and on many occasions he addressed from the chair the fellows and members

Behind the public figure there remained the man, and of him his friend T J H writes

Walter Elliot carried his sense of fun through every phase of his career His interests were multiple and if he took up a subject he made it his business to master it He was a friendly man, and although as a public figure he had his critics, over the years he never lost his capacity for making and holding friendships The distinctions and honours which were conferred on him reflect in some measure the great services so cheerfully given in and out of office, academic and political He was bound to meet with disappointments and frustrations, but he appeared to regard them as part of the art of living, and never permitted sourness, bitterness or regret to mar his countenance or speech A very full life has reached its close In many and different circles, particularly in Scotland where he was respected, admired, and loved, it will be a long time before we become accustomed to the idea that Walter Elliot is no longer with us

Elliot died on Jan 8 at his home in the Borders and is survived by his second wife, formerly Miss Katharine Tennant

Miss EDITH HALL

H M M M writes

Edith Hall was elected obstetric surgeon to the Mothers' Hospital, London, in 1923 She held this post for about 26 years and was latterly chairman of the medical committee Her warm human kindness, understanding, and integrity earned the affection of all who knew her, and her obstetric and gynæcological skill and judgment won the confidence of those who worked for or with her At the end of a hectic day, one of her registrars remarked that when obstetric emergencies and anxieties piled up in the wards and labour-rooms, the arrival of Miss Hall in the hospital brought immediate relief and a sense of calm—a spontaneous tribute which reflects the remarkable influence she possessed, as well as being a tribute to her outstanding ability as an obstetrician Her wisdom and personality were a valued asset both to the Mothers' Hospital and to her colleagues, and her resignation, when she found her professional burden too heavy, was a lasting loss The sympathy of all who knew her goes out to her sister and close friend, Dr Marjorie Hall

Appointments

BEIRNE, EILEEN M, M B N U I, D C H, D P H assistant divisional M O, Lancashire

JACOBS, RACHEL, M D Prague, D P H, D OBST assistant M O (administrative), West Ham

MCNAMARA, HILDA E., L.M S Newfld, D P H, D OBST assistant divisional M.O, Lancashire

MANN, G E, B.M Oxon, F R C.S, D L O part time consultant E N T surgeon, Chesterfield Royal Hospital

MARTIN, ALBERT, M B Birm assistant M O H, Sutton Coldfield

PINKERTON, ISABELLA M, M B Wales, D P H assistant M O, High Wycombe area

TWEEDY, P S, M D Lond, M R C.P physician (S H M O), geriatric unit, Newcastle group of hospitals

Births, Marriages, and Deaths

DEATHS

MEREWETHER —On Jan 7, at the Royal Victoria Hospital, Folkestone, Henry Osborne MacCabe Merewether, O B E, F R C.S E, of Lympne Hall, Lympne, Kent

Notes and News

CONTROL OF NARCOTICS

In its report[1] for 1957, the Permanent Central Opium Board of the United Nations says that the operation of the system of control of narcotics has improved in the past five years, statistics have been fuller, more accurate, and more promptly submitted, though some countries cooperate less well than others The board deals with *all* narcotic drugs

One of the effects of the controls introduced in 1925 and 1931 has been that it is now almost impossible for addicts to get narcotics from legal sources The legal production is virtually limited to medical and scientific needs, except in the case of coca leaves and cannabis, the quantity of coca leaves produced for chewing is unknown but was not less than 9600 tons in 1956 (thirty times the production for medical use) From 1955 to 1956 the quantity of opium produced decreased, while the amount used in medicine increased Only three countries manufactured heroin in 1956, and the international trade was negligible (1 kg) 32 synthetic narcotic drugs were controlled by 1956, pethidine is by far the most commonly used, the United States accounting for two-thirds of world consumption.

NOTIFICATION OF ACUTE RHEUMATISM

Under the Acute Rheumatism Regulations, 1953, the disease must be notified in Cornwall, parts of Lindsey, the county boroughs of Bristol, Grimsby, Hull, Lincoln, Salford, and Sheffield, and the borough of Ilford These regulations have now been extended indefinitely It is possible, the Ministry of Health says, that the areas in which the disease is notifiable may later be increased

LESSONS IN REPRODUCTION

There has appeared a sprightly little picture-book[2] of first lessons in human reproduction and sex for four-to-eight-year-olds and their parents The line drawings, by Gerda Nystad, of children and young adults, clothed and naked, are modest and pleasing, and the text shows well how to say enough and not too much to the inquiring child The sketch of the unborn at ease in a womb without exit but pierced by an umbilical feed-pipe seems a little fanciful in such factual context, but the book should both please and profit those it is meant for

NEW MEDICAL FILMS

Acidity, Dyspepsia, and Peptic Ulcer (16 mm , sound, colour, 28 min , Britain, 1957) presents dyspepsia as an imbalance between gastric acidity and tissue resistance

It shows that statistically there is a relationship between acidity and the incidence of peptic ulcer, but ulcers that arise where acidity is normal indicate a low tissue resistance Methods of measuring gastric acidity are shown and the histamine response is described. In the second half of the film the cause of pain is considered and methods of reducing the acidity mentioned Finally, the advantages are set out of a proprietary preparation for this purpose

The film gives a concise exposition on the modern view of dyspepsia but the emphasis on a particular treatment detracts from the value of the film for teaching purposes The commentary is excellent and carries the weight of the exposition The picture is largely diagrammatic and at times the artist seems to be hard pressed to fill the screen with appropriate symbols to match the lecture. The film may be obtained free from C L Bencard, Ltd , *Minerva-road*, Park Royal, London, N W 10

The Manchester Regional Hospital Board is responsible for a film, *There was a Door* (35 mm , sound, black and white, 30 min , Britain, 1957), on mental deficiency

Taking as its text " It is not in the best interests of patients fit to live in the general community that they should live in large and remote institutions—cut off from the world " (from the report of the Royal Commission on Mental Illness) the film discusses the problem of the overcrowding of hospitals with mentally deficient patients, many of whom could be trained to undertake suitable work and live at home. The training centre at Oldham is described, and municipal and county authorities are encouraged to set up similar centres for the training of mental defectives in their areas

The film puts extremely well the case for keeping mentally defective patients out of hospital, this coincides with the recommendation of the Royal Commission, though the film was in production before the report was published The film is designed primarily for local health authorities, and it is therefore surprising that some patients with extreme mental deficiency, who are unsuitable for training, are shown in the film. Indeed the film should be very carefully introduced when shown to non-medical audiences The production is of professional standard. The film is available on hire from Sound Services, Ltd , 269, Kingston Road, London, S W 19 16 mm prints will probably be available shortly

Nobecutane—A Plastic Surgical Dressing (16 mm., sound, colour, 23 min , Britain, 1957) describes the properties and uses of the plastic skin dressing in surgery and other fields

The film mentions its advantages over conventional dressings, and shows in detail its application to an operation wound and the subsequent removal of sutures Other varied situations are named where the dressing has proved valuable, and the film ends with a summary of its properties

This is a very good film that convincingly presents the advantages of the plastic dressing A black and white sequence of the Korean war could be omitted, but otherwise the pictures and commentary contribute equally to the smooth exposition The colour photography is excellent and the commentary authoritative and clear The film is available free from the Film Library, Evans Medical Supplies, Ltd., Liverpool

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University of London

On Dec 18 the degree of M D was conferred on F W O'Grady

University of Bristol

The following have been approved for the degree of M D

A J Coppen, D G Davies, G Walters

Order of St John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this Order

As Knights—J T Whitley, O B E , M B , R. V S Cooper, M.B

As Commanders (Brothers)—Sir Geoffrey Todd, K.C.V O , O B E., F.R.C.P , Sir Charles Dodds, M V O , F R.C.P , F R.S , D P McIntyre, F R.C.S E , J C R. Buchanan, C.M G , M D , F R.C.P , C H Drake, M R C.S , D W Montgomery, M D , F R.C.S I , M Y Paget, M R.C.S , Air Vice-Marshal L M Corbet, C.B E., M B , George Swapp, D C.M , M M , M.B , H H Hurst, M.B

As Officers—H D Teare, M B , Squadron-Leader Philip Cauthery, M.B , William Duncan, M B , C T Newnham, M R C.S , Alexander Morrison, L.R.C.P , Alexander Chalmers, M B , C F Fairlie M.D , T D , A. G Walker, M.B , R G Sprenger M.B , R H Kipping, M B , R. H Scott, M.R.C.S , S W Cooper, F R C.S , J H C. Clarke, M B , G N M. Wishart, M R C.S , F P Wallis, M.R C.S , S G Nelson, M B., J M Pedler, M B , N G Hoddle, M B , M. F Leslie, M.B

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold a public hearing on Thursday, Jan. 23, at Church House, Great Smith Street, London, S W 1, at 11 15 A.M Representatives of the British Medical Association have been invited to attend

International College of Surgeons

Forthcoming meetings of the college include a scientific trip to the United States, leaving about March 1 and returning about March 22, and a meeting in Brussels from May 15 to 18 Further particulars may be had from Dr J F Brailsford, 20, Highfield Road, Edgbaston, Birmingham 15

World Federation for Mental Health

On Jan 24 Dr Brock Chisholm, president of the World Federation for Mental Health, will speak at Leeds on Human Problems of the Atomic Age This will be the annual public lecture arranged by the United Kingdom committee of the Federation It will be given in the great hall of the University of Leeds at 6 P.M , and tickets may be had for 2*s* 6*d* from the northern secretary, National Association for Mental Health, 9, Mount Preston, Leeds, 2

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[1] Permanent Central Opium Board Report to the Economic and Social Council on the Work of the Board in 1957 United Nations Geneva, 1958 Pp 83 5*s* 6*d* Obtainable from H.M Stationery Office, P O Box 569 London S E.1

[2] Peter and Caroline A child asks about childbirth and sex. By Sten Hegeler. London Tavistock Publications Ltd 1957 Pp 29 7*s* 6*d*.

Royal College of Surgeons of England

At a meeting of the council on Jan 9, with Sir James Paterson Ross, the president, in the chair, Mr B K Rank, of Melbourne, was appointed Sir Arthur Sims Commonwealth travelling professor for 1958 Dr G S W Organe was appointed Joseph Clover lecturer for 1959

Dr C A Keele was elected to the fellowship of the Faculty of Anæsthetists A diploma of fellowship was granted to A B Cassie, *and a diploma* of membership to V P Nagpal

The following diplomas were granted jointly with the Royal College of Physicians

D L O—Paul Abbey, Rasheed Ahmad, Z H Alvi, Julian Bihari, Thomas Cartmill, R R A Coles, B R Das, M J D Cruz, J L Golden, John Hall-Jones, Martin Horowitz, Y P Kapur, G M Khan, F W Kwok, Ishwar Narain, N B Parvathiah, Jeffery Potter, L N Prasad, Rajendra Prasad, I P C Robertson, D S Sardana

D A—F D Adrianvala, Eleanor K Althorp, Edna W Anthony, N K Ashurst, Roma M Bedford, Abraham Berry, Jane I K Binnie, H L Blake, Margaret A E Boyce, J H Breed, R A Butler, P H Byles, Joan M Byrne, Po Sing Chau, J M Clark, R J Clark, W H Cochrane, G F Conway, S K Coombes, H B Coulter, Bridget M Cowley, H J L Craig, J P Czyniewski, M A de Valero Wills, B J Dolan, R R Evans, A D J Farquharson, M E Fielding, G Flowers, H J Freedman, B L Gupta, V G Gurjar, Christopher Gyaw, R W Hall, D D Hart, D F Hogan, Margaret C Holderness, W G Holland, Ann Horsburgh, T H Howells, Ayesha S Ishrat Husain, M O N Iyengar, T E Jones, V R Jones, Kathleen E Kennedy, J C Kennedy Smith, J D Kinnell, R J Knight, H P Lacey, R Grove Lacey, Anatol Lagowski, G L F Lau, P D Lawler, J L Layng, Phyllis L Liddle, G J M Lincoln, J V McCooey, P W McCormick, S W McGowan, N N Madan, R E W Manley, R R Manning, Maung U Win, T W P Millar, J S Miller, Mary H Miller, D R Morgan, Ada C Morrison, Joyce Newman, B A Nixon, Krishnapathee Parbhoo, T F J Parker, A S Paton P A P Pompa, Diana Ratcliffe, D D G Simpson, Chanan Singh, Harold Slomowitz, J A Stainton Ellis, K D Stephenson, C R Sulochana, N S Thomas, J S Toner, Patricia A Topham, Sohrab Rustomji Umrigar, R D Unkles, Sariphorn Vanikieti, F H Walter, Elizabeth M B Watson, A I Weinreich, J M S Whiting, D C M Wilcox, P F Willis, J E York, Freda Young

D M R D—D A Alderson, Keith Ashcroft, Kyaw Aung, W R Barrow, D C Bernstein, M P Bhalla, Savas Bissylass, H J Bloch, Ronald Cable, D F Cantwell, George Cohen, I D Davies, M L Dyson, R F Fouche, John Fraser, R W Galloway, J J Gately, Kenneth Grainger, Ian Isherwood, Naphtali Joffe, Brigid Keane, J T Lamb, James Lees, J J D Lobo, A B McGrigor, M R H Mahmood, R C Michell, N L Mills, Israel Movsas, N D C O'Connell, Irmgard Patton, J J Prior, K D Reddy, Percy Reichman, Broughton Ridgway, J H Rustage, Ahmed Sardar, H M Saxton, S N Sender, M P Shannon, Eli Sheville, M J Strachan, H M Strathern D F Street, Geoffrey Sullivan, S N B Talwatte, Sneh Taneja, R P Vass, Peter Ward, W L Wong

D P M—G H Armitage, Grace Bainbridge, A H Borowitz, A M Bradfield, S W G Caseley, M R Chaudhry, A B Cooper, F H Corbitt, J McK Davie, R N Davis, Joseph Erulkar, G W Fenton, Albert Gage, M E Grant, Ian Hadfield, Lewis Harris, Peter Hays, G A Heasman, Mary K P Henderson, William Leggat, Kypros Loucas, N C Low, S M Macentee, N K Macrae-Gibson, W K Marshall, Pamela G L W Mason, W J Nicholson, V R Ntsekhe, P M J O'Brien J R Palmer, Barbara Petrovskaia, Abe Pick, E W Poole, J H Price, J R Roy, Barbara J Salisbury, G H Scott, J C Scott, Karam Singh, W B Spry, J S Stead, A A Sugerman, S S Syalee, W D Wilson, Waclaw Wollen

D T M & H—H F McElligott, Umasanker Sahay, Thambo Tharmaratnam

D Path—B B Beeson, P W J Bosman, S M Deoras, Geoffrey Garrett, Barbara E Grahame, I J Hunter, Felix Kurrein, C J McDonald, James Ward

D P H—Mary M M Boyd, M J Catton, M L Graeme, Bashir Hussain, P V Krishnamurti, C L Milburn, S K Sen, Tin U, E J Wright

National Association for Mental Health

This association is holding a conference on the report of the Royal Commission on the law relating to mental illness and mental deficiency, on *March 6* and 7, at Church House, Westminster, S W 1

The speakers will include Dr W A L Bowen, Dr D H Clark, Dr J D Kershaw, and Dr Denis Leigh Further particulars may be had from the conference secretary of the association, 39, Queen Anne Street, W 1

Chronic Rheumatic Diseases

A weekend course with lectures, ward rounds, and practical demonstrations will be held at the rheumatism unit of St Stephen's Hospital *on March 15* and 16

Professor J Trueta will open the course, and the speakers will include Dr Francis Bach, Dr Grace Batten, Dr Raymond Daley, Dr Philip Ellman, Mr H E Harding, Dr F Dudley Hart, Dr R H Marten, Mr G Pritchard, and Dr Gordon Signy Further particulars can be obtained from the secretary, Fellowship of Postgraduate Medicine, 60, Portland-place, W 1

Appointment in Northern Ireland

Dr W McCartan, who recently retired from the post of physician-superintendent of St Francis and Hurstwood Park Hospitals, Haywards Heath, has been appointed medical inspector of mental hospitals in Northern Ireland in succession to Dr F G L Barnes

International Congress of Physiological Sciences

This congress will be held in Buenos Aires from Aug 9 to 15, 1959 Further particulars may be had from the secretary, Facultad de Ciencias Medicas, Paraguay, 2151

London Skin Hospital

In accordance with the decision of the North West Metropolitan Regional Hospital Board, this hospital will be closed for *the* treatment of skin conditions on *March 31* Patients still under treatment at that date will be referred to their general practitioners New patients will not be accepted after Feb 14

Dr J A Fraser Roberts has been elected president of the Royal Anthropological Institute

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CORRIGENDUM *New Year Honours*—We regret that through our mistake the name of Dr Clarence Smith appeared twice in our list of medical honours (Jan 11, p 100) Dr Smith in fact was appointed O B E

Diary of the Week

JANUARY 19 TO 25

Monday, 20th

HUNTERIAN SOCIETY
8 30 P M (Mansion House, E C 4) Sir Ernest Rock Carling Biological Systems and Atomic Radiation (Hunterian lecture)

Tuesday, 21st

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Pathology* Prof J Firket (Liège) Cancer of the Lung in the *Industrial Area of Liège* during Recent Years
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr L H Gray Influence of Oxygen on the Response of Cells and Tissues to Ionising Radiation
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Prof Charles Rob Ileus
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
5 30 P M Prof F C Ormerod Sinusitis
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R H Meara Skin Diseases in Children I
SOCIETY FOR THE STUDY OF ADDICTION
8 P M (11, Chandos Street, W 1) Sir Adolphe Abrahams Use and Abuse of Drugs by Athletes
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) Prof Robert Platt, F R C P Darwin, Mendel, and Galton
UNIVERSITY OF ST ANDREWS, Queen's College, Dundee
5 P M Prof A E Ritchie Methods of Artificial Stimulation and Potential Recording in Neuromuscular Disorders

Wednesday, 22nd

ROYAL SOCIETY OF MEDICINE
5 P M *Endocrinology* Dr Sheila Sherlock, Dr Julius Lee, Dr G W Bisset, Dr W H Summerskill Endocrine Changes in Liver Disease
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M Dr R R Race Contributions of Blood Groups to Human Genetics
INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P M Sir Russell Brock Basic Principles in Heart Surgery
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Cellular Nævi
NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY, 64 St James's Street, Nottingham
8 30 P M *Dr C A Boucher Accidents in the Home*
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School) *Medicine and Pathology* Prof Alexander Haddow Recent Trends in Cancer Research

Thursday, 23rd

UNIVERSITY COLLEGE LONDON, Gower Street W C 1
5 P M Dr E Lester Smith Biochemical Functions of Vitamin B_{12}
ROYAL SOCIETY OF MEDICINE
8 P M *Urology* Prof N F Maclagan Urinary Colloids Mr J H Carver Bilateral Orchidopexy and Fertility Mr Norman Slade *Bacteræmia and Septicæmia* after Urological Operations
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Mr A F Huxley Excitation and Contraction in Voluntary Muscle
INSTITUTE OF DERMATOLOGY
5.30 P M Dr Meara Skin Diseases in Children II
NUFFIELD ORTHOPAEDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8 30 P M Dr J D Mineiro Arteriography in Orthopædic Surgery
LIVERPOOL MEDICAL INSTITUTION, 114 Mount Pleasant, Liverpool, 3
8 P M Dr Philip Robinson, Dr A Thelwall Jones, Dr Leonard Findlay Care of the Aged
UNIVERSITY OF ST ANDREWS, Queen's College, Dundee
5 P M Prof H P Gilding Capillary Circulation and Tissue Fluid Exchange

Friday, 24th

ROYAL SOCIETY OF MEDICINE
5 P M *Pædiatrics* Dr C A Boucher Mr Douglas Jackson Prevention of Accidents in Childhood
POSTGRADUATE MEDICAL SCHOOL
10 A M Mr T G I James Spinal Cord Tumours
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3 30 P M Mr N Asherson Deafness
5 30 P M Mr G H Howells Malignant Diseases of the Accessory *Sinuses*

The Lancet · Saturday 25 January 1958

BETWEEN GUESSWORK AND CERTAINTY IN PSYCHIATRY *

AUBREY LEWIS
M.D. Adelaide, F.R.C.P
PROFESSOR OF PSYCHIATRY, UNIVERSITY OF LONDON

IT is the common state of reflective and inquiring minds to be somewhere between untrammelled guesswork and certainty It would be discreditable if psychiatrists were huddled at either extreme, wholly engaged in guessing or ignorantly certain We are, however, sometimes suspected of luxuriant speculation and of invincible faith in our tenets and I propose to consider how this reputation has arisen

More than most branches of medicine, psychiatry can be regarded as an art One of its distinctive procedures—psychotherapy—manifestly depends on subtle relationships and incommunicable qualities of personality But in the proportion that it is an art, psychiatry is a weak branch of medicine and the constant aim of those who would further and strengthen it is to apply to it the methods of scientific inquiry If these result in encroachments on the area reserved for the art of medicine, and substitute assured knowledge for assumptions and intuitions, so much the better This is not to deny the large part which compassion and human feeling must play in the care of mental disorder its history attests that they will always be necessary, but they operate in a territory that must be explored and charted Psychiatry in this is like the rest of medicine, combining moral and personal principles of action with those arrived at by the methods of science, and depending on the last for any increase in its power to prevent and control disease

There is a large subcontinent of psychiatric research which is concerned with applying the methods of the natural sciences to morbid phenomena—biochemical and physiological investigations in mental disorder are obviously of this nature Psychological and sociological inquiries are in another area, that of the social sciences Many studies in psychiatry lie in both areas—because they are intermediate, as physiological psychology is, or because they are carried out through joint activities Much controversy has centred on differences between the methods of the natural sciences and of the social sciences, stressing the relative weakness of the latter Weaknesses in the social sciences—immaturity in their *technical* procedures, laxity in their theorising—*will tell* heavily against psychiatric advance It is true that some psychiatrists distrust the social sciences so much that any excursion in that direction is for them tantamount to walking the plank Nevertheless the part that psychology and sociology must play in the advancement of psychiatry is undeniable

Though there is manifest convenience in distinguishing between the natural and the social sciences, fundamental difference between them cannot be discerned The slower tempo of development in the social sciences, and the immense difficulties in the way of measuring and controlling the phenomena they study, cannot be gainsaid, but the social, like the natural, sciences depend on sense-data, are nourished on hypotheses, and ask to be continually corrected through experiment and enlarged through further observation If psychiatry were to put all its hopes in the application of the natural sciences and were to claim exemption from the discipline of the social sciences, it would be aligning itself, along a large stretch of its front, with *dead philosophies* and cults in which doubt is repudiated for the sake of a limited and spurious inner consistency

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The scientific method, which has been so closely studied of late by philosophers, is not, of course, the preserve of the natural sciences (though to them it owes its enormous prestige) Whether in the physical, the biological, or the social sciences, there is the same essential passage from untested guess to tenable, unfalsified conclusion—which may be, rather loosely, called a confirmed conclusion or a certainty, in the sense in which the circulation of the blood is a certainty The initial hypothesis is arrived at by divers routes, about which on the whole little is known deductions from it entail predictions which are put to the test of direct observation or contrived experiment and when enough evidence in support of the hypothesis has accumulated, it is given provisional acceptance In time statements are thus arrived at which embrace and order very many facts, these statements have always started as hypotheses, plausible guesses

It is a commonplace that hypotheses are indispensable for scientific activity, and that hypotheses must be judged by their heuristic as much as by their veridical importance inadequate or false hypothesis may have value in provoking further observation and experiment. "Even *mistaken* hypotheses are of use in leading to discoveries", wrote Claude Bernard "It seems indeed a necessary weakness of our mind to be able to reach truth only across a multitude of errors and obstacles" De Morgan put it in a telling paradox—"Wrong hypotheses, rightly worked, have produced more useful results than unguided observations" the phlogiston theory or the corpuscular theory of light illustrates his point It is equally a commonplace, however, that hypotheses are an impediment to knowledge when they are so loosely formulated that we cannot deduce their logical consequences and therefore cannot make predictive statements which could be verified or refuted, the systematists of the 18th century exemplified this in medicine Moreover, it is a poor recommendation in favour of a certain hypothesis to say that it explains all we know, for, as Karl Popper emphasises, it is only by testing it on seemingly contrary instances that we can carry out that determined effort at refutation which is what we really mean when we speak of verifying a hypothesis Interpretations which explain the phenomena only too readily, lead to a feeling of certainty which *closes* the mind to further inquiry and makes the believer hostile to any breath of scepticism

I mention these familiar considerations because they have a direct relevance to some puzzling features in the development of psychiatry In spite of the sophistication apparent in its literature, psychiatry is in some important respects struggling with problems which beset the physical sciences three hundred years ago The word "hypothesis" was a bad word in the 17th century.

"Hypotheses non fingo", said Newton "Hypotheses, *whether metaphysical* or physical, have no place *in science*" (Quicquid enim ex phenomenis non deducitur hypothesis vocanda est, et hypotheses seu metaphysicae seu physicae seu qualitatum occultarum seu mechanicae in philosophia experimentali locum non habent) Indeed, Newton lost no opportunity to belittle them, as in a letter to Oldenburg in 1672 where he wrote "I do not think it needful to explicate my doctrine (of colours) by any hypotheses at all You see therefore how much it is besides the business in hand to dispute about hypothesis For which reason I shall now proceed to abstract the difficulties involved in Mr Hooke's discourse, and without having regard to any hypothesis consider them in general terms "

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* The Bradshaw lecture for 1957, delivered before the Royal College of Physicians on Nov 7

It is a little odd that the most illustrious scientist whom England has produced should have spurned what men now regard as an essential element in the process of arriving at truth Surely a semantic misunderstanding But a widespread one Let us look at a great medical contemporary of Newton's Thomas Sydenham wrote, in the Preface to his Observations, that hypotheses should be laid aside, in the study and description of diseases, "for 'tis difficult to give a detail of the errors that spring from hypotheses, whilst writers, misled by these, assign such phenomena for diseases as never existed but in their own brains", and similarly, in his letter to Dr Paman, he speaks sharply of the many authors whose "writings are founded upon Hypotheses which are the result of a luxuriant imagination, and the symptoms of diseases (wherein their true history consists) as described by them, appear to be deduced from the same source, and the method of cure, also, is derived from the same fictitious principles, and not from real facts, and thus becomes most destructive to mankind, so full of specious reasoning is every page of the writings of such superficial men, whilst the directions of nature are overlooked "

A hundred years later Pinel was still writing in the same strain, rejecting "toute discussion métaphysique, toute hypothèse sur la nature des fonctions intellectuelles ou affectives, sur leur genération, leur ordre, leur enchaînement réciproque "

It is plain that in those days hypotheses had a bad name because they connoted speculative propositions, so tenaciously held that conclusions derived from observation were rejected if they conflicted with them It might be assumed that hypotheses no longer carry this taint Yet in the introduction to a recent English textbook the authors review the requirements for a scientific approach and then say

> "It is embarrassing that such basic ideas of scientific method should have to be repeated and discussed in a textbook of psychiatry, but not one of these requirements is met by a very large part of the contributions which are made to contemporary psychiatric literature Hypotheses are reared in a vacuum without logical basis, and are expressed in imprecise phraseology in terms which have not been defined They are often so vague that it is impossible to draw logical consequences, but even when that can be done critical investigations are not made (Workers') hypotheses serve the single aim of providing a framework for interpretation " (Mayer-Gross, Slater, and Roth 1954)

These strictures echo the complaints from the 17th century and are voiced, from a more detached standpoint, by a medical historian reviewing the theory of psychoanalysis

> "a 'system' explaining in logical sequence the origin, nature and treatment of all disorders of a given class is suggestive—within the mental field—", says Richard Shryock, "of those general medical systems which were so typical of the eighteenth and earlier centuries If, like the latter, psychoanalysis cannot be checked one way or the other, it represents a reversion to the system-making stage in medical methodology, and may be expected to reproduce the various features and developments typical of that level It is suggestive that this is indeed just what has happened Once more, within this particular field, one hears of masters and disciples, of divergent 'schools', of scientific controversies in which there is an 'attack' or a 'defence' of a given system, with more or less feeling on both sides "

A more recent censure, by outspoken psychiatrists, is that of Lemkau and Pasamanick, who, contemplating the preventive powers at our disposal, wrote in 1953

> "The flashes of insight that have characterized the great leaders of our field in the past must be documented painstakingly with proof, a type of scientific discipline of which psychiatrists are perhaps more derogatory than appreciative "

Whether these severe judgments are unfair is less important than that they repeat a pattern of criticism which is neither unfamiliar, nor confined to psychiatry and psychoanalysis Historians have similar hard things to say about Prof Arnold Toynbee Sociologists note such frailties in other sociologists And in the most entrenched and assured branches of medicine critics sometimes discern them too As an unsparing observer of loose thinking in medicine noted, the dividing wall between an unconfirmed hypothesis and a valid explanation often disappears, especially in therapeutics, because autistic aims prevail over rational thought (Bleuler 1927). This is nothing new "the human understanding resembles not a dry light, but admits a tincture of the will and the passions for man always believes more readily that which he prefers his feelings imbue and corrupt his understanding "

* * *

It would be easy to pile up instances showing that psychiatry is not the only branch of medicine—or of knowledge—to be pilloried for lax thinking and complacent dogmatism It has, however, troubles which seem peculiar to itself, and some ministrants who seem peculiarly indifferent to the scientific method as understood by the rest of the world Nevertheless, I doubt if these are special characteristics psychiatry's troubles are those inherent in the study and improvement of human behaviour, psychiatrists are for the most part bent, like other doctors, on doing their best for patients according to current methods and theories, without stopping to pick up and examine the little hedgehogs of doubt that sit by the therapist's path There is nothing specially psychiatric about that Besides those undoubting psychiatrists engaged mainly in treatment, there are in many countries psychiatric investigators fully alive to the rigorous demands of research but equally alive to the extreme complexity of their problems

This complexity can be well seen when the value of treatment is reviewed It has been said that "psychotherapy is where organic medicine was in the days of Paracelsus" this gross exaggeration attests the gloom which some feel when they try to judge the present position of psychotherapy, and indeed of psychiatric treatment in general Has the psychiatrist culpably failed to observe elementary principles of trial and evaluation, or has he attempted the task but found it too formidable? The question is not a rhetorical one To answer it, the evaluation of psychiatric treatment has to be looked at more closely

* * *

The aims of medical treatment are ordinarily to remove or lessen disabilities and pain, to put an end to morbid changes in the patient's body of which he may not be aware but which must sooner or later cause disability, and, thirdly, to enable him to live as satisfying a life as possible, in spite of persistent disability and morbid process Applied to mental illness, all this becomes equivocal The patient will often be unaware of disturbances very plain to others, he may not complain of his symptoms, he may even cherish them He may lead a less satisfying life when his symptoms have been got rid of than when he had them. The morbid process often has no physical substrate that we know of and the psychopathology may be obscure and inaccessible The criteria of recovery are therefore hard to specify, and, like the criteria of improvement depend on an assessment of the patient's happiness, competence, and wellbeing which involves moral and social values as well as plainly medical ones It must moreover be a comparative assessment, since if the patient was a poor creature—an inadequate psychopath as people now say—before his attack of anxiety and depression came on, it must be counted as recovery if he reverts to his previous state, free again from manifest anxiety and depression, though in another man, previously better equipped to fulfil his social role, an illness that subsided leaving him in a state of inadequacy and social malaise would be rightly regarded as having a bad outcome.

A rather silly but often repeated truism says that the aim of psychiatric treatment is to promote mental health It is hard to tell what the latter phrase means Mental health is an invincibly obscure concept. Those who have attempted to define it in positive terms have twisted ropes of sand, telling us, for example, that a man's mental health consists in

> " (a) active adjustment or attempts at mastery of his environment as distinct both from his inability to adjust and from his indiscriminate adjustment through passive acceptance of environmental conditions, (b) unity of his personality, the maintenance of a stable, internal integration which remains intact notwithstanding the flexibility of behaviour which derives from active adjustment, and (c) ability to perceive correctly the world and himself "

This clutter of words is groping towards an ideal, a sociological ideal but much of it can have no operational referents and it abounds in terms which are undefined and at present undefinable. Most of those who state criteria of mental health follow the lead of the World Health Organisation in refusing to take the absence of disease or infirmity as the characteristic feature, they do not say a man is well when he is free from manifest illness but speak instead of " optimal growth and happiness of the individual ", " full maturity ", " adjustment to the world and to each other with a maximum of effectiveness and happiness ", using quantitative words like " full " and "maximum" to qualify immeasurable states like happiness

* * *

Mental health, we may conclude, is an abstraction which is very loosely interpreted We cannot in every case decide, by comparing the degree of mental health after an illness with that before, whether the patient has recovered, or whether his illness has improved, or is stationary, or worse

It is of course true that in many instances such a difficulty hardly enters anybody's mind, since there is an undeniable change for better or worse in the patient's condition, and everybody entitled to express an opinion—the patient, his relatives and intimates, his doctor—will concur But these cases are not, I think, the majority With an illness such as schizophrenia, or still more perhaps with many neurotic disorders, the issue is not clear cut, there may be sharp differences of judgment about outcome. One psychiatrist can report a rich harvest of recoveries in a series of patients whom another, equally sincere and observant would describe as partial failures of treatment.

This is indeed an obstacle which will persist so long as we have no satisfactory measures of clinical change There is another, worse obstacle—uncertainty as to what would have happened if the treatment had not been administered " We cannot judge the influence of a remedy on the course and outcome of a disease if we do not previously know the natural course and outcome of the disease " The course of a mental illness is affected by so many factors, within the patient and in his environment, it is so subject to unforeseen turns of fortune that a change cannot safely be attributed to therapeutic intervention unless it is frequently and regularly produced or comes prompt on the heels of the treatment. This is of course a common difficulty in therapeutics which can be overcome by rigorous trials using, as controls, patients closely comparable to those who are treated But matching psychiatric groups for this purpose is a daunting business, since they should at least be alike in the distribution of sex, age, intelligence, duration of illness, form and severity of illness, and previous treatment alike also in the physical, and still more the psychological circumstances of their medical and nursing care, except for the particular therapeutic procedure that is on trial It is an exacting affair to match for form and severity patients with illnesses whose somatic pathology is not known and the symptoms of which can be elicited fully only with the patient's concurrence—a requirement often unfulfilled The therapeutic zeal of psychiatrists, now as great as was once their nihilism, militates also against painstaking trial and provisional judgment of various methods of treatment a difficulty in other branches of medicine, too

The delay caused by these impediments is evident in the confused verdict on hypoglycaemic treatment of schizophrenia with insulin Here is a method that has been before the world for over twenty years, widely employed in all civilised countries, and the subject of hundreds of experiments and technical reports Yet it is still in such a dubious state that one can read responsible statements declaring on the one hand that it is " the only effective method of treating early schizophrenia " and, on the other, that " there is no significant difference in the outcome of treatment (of schizophrenia) whether unconsciousness has been induced by insulin or by barbiturates" Leucotomy is in rather similar case, and the medley of " tranquillising " drugs may pass, though more rapidly, into the like chiaroscuro of approval and rejection

* * *

But the doubts which attend physical methods of treatment are dwarfish alongside the giant misgivings and disputes which envelop psychotherapy in dust and fog The trouble is of long standing, and has divided psychiatrists bitterly In the Bradshaw lecture of 1936, the psychiatrist who delivered it said

> " There is practically no evidence in existence as to the efficacy of psychotherapy which is guarded against fallacy in such a way as would entitle it to serious consideration in a court of law Among those ' cured ' by any novel remedy are those who have never had the disease, those who still have it, those who have never had the treatment, and those who would have recovered equally well without it. All these classes are generously represented among those cured by psychotherapy "

After this pungent and uncompromising passage, Professor Mapother went on to express his qualified belief in the usefulness of psychotherapy

' it is time to recognise ', he said, " that the hard-boiled disbeliever in psychotherapy is as dead as Queen Anne The real division is between those who are contented and discontented with the fumblings at present enjoying the name. It would be absurd to deny a certain limited efficacy to psychotherapy."

Since then belief in the efficacy of psychotherapy has become much more general among psychiatrists, and valuable systematic observations like those of Whitehorn and Betz have become available. But the same note, with modifications, can be heard in the following passage from a recent paper by two prominent American psychiatrists:

> "We do have the firmest kind of conviction that psychotherapy carried on under the aegis of medicine provides a type of help which is of the first order of importance. But while admitting the importance and efficacy of psychotherapy in its many forms, we cannot emphasise too strongly the necessity for being as rigorous as possible when we make scientific judgments about the methods, goals and effectiveness of psychotherapy" (Bowman and Rose 1954).

This attitude, moreover, is found among psychiatrists who are constantly engaged in psychotherapy. Thus a veteran psychoanalyst, C. P. Oberndorf, acknowledged the many obscure aspects and unpredictability of treatment, about which psychoanalysts themselves were not agreed, and urged the need for a planned investigation of the results of psychoanalysis.

The psychiatrists I have referred to—and, I should think, the great majority of psychiatrists everywhere—are convinced that psychotherapy is beneficial. But which patients it will benefit, what changes it will effect, whether one form of psychotherapy is more effective than another and if so for which types of illness—these are questions they ask themselves with varying insistence and frustration, distrusting their personal opinions on a matter of this kind, and distrusting the consensus of their fellow experts equally or more—since they know enough of the history of medicine and of human illusions to be aware that what most people are convinced of at a given time is not necessarily true.

Psychiatrists have not yet succeeded in investigating the efficacy of specified forms of psychological treatment for specified mental disorders in a way which satisfies the customary requirements of scientific evidence.

Besides the reasons I have been mentioning, there is the difficulty of accumulating a sufficient number of treated and untreated patients and of withholding treatment which patients desire and which their doctors think would benefit them. Psychotherapy, in its most widely known form—i.e., psychoanalysis—may go on for years, and is more often than not carried out in private practice. To collect the requisite number of comparable patients entails the cooperation of a number of psychiatrists engaged in psychotherapy and requires that their patients should be willingly available for independent examination at various phases of their treatment.

Psychotherapists are seldom sceptical or, as one might say, ambivalent about the treatment they give, and "philosophic doubt" is not in keeping with their metier, many of them would desist from psychotherapy if they ceased to be sure that it is effective. It is therefore asking a great deal to invite them to cooperate, at this time of day, in trying to find out whether they may be deceiving themselves as to the usefulness of their life's work. In my own experience, it has not proved possible to get groups of psychotherapists committed to an adequate planned investigation into the results of their treatment.

Among the main problems to be solved if such an investigation is to succeed are how to measure mental change and how to predict mental illness. Now the measurement of mental functions is an enterprise to which psychologists have addressed themselves with brilliant success, and the prediction of behaviour on actuarial lines has been developed by psychologists also, as the names of T. R. Sarbin, Philip Vernon, and Paul Meehl remind us. It would be natural therefore for psychiatrists to have prayed in aid of psychologists here for flattening the major obstacles and designing the whole investigation with that scientific detachment which psychologists may be supposed to possess in high degree.

Detachment is not always evident in psychologists when they concern themselves with psychotherapy. Some immerse themselves in it wholeheartedly as practitioners, on the American pattern. Others sedulously contemplate the pretensions of psychotherapy, shudder, and denounce its hollowness, they are drawn to it by a fascination like that which God has for atheists. But even if psychologists are sometimes emotionally involved, just as psychiatrists are, there is no doubt that they can contribute notably to the elucidation of a problem which everyone must wish to see solved. They have in fact tackled it, if C. R. Rogers' "client-centred" counselling is to be reckoned as a form of psychotherapy. Their skills are relevant, and in my view indispensable, if we are to emerge from the existing morass—as indispensable as the skills of the psychiatrist. By emergence from the existing morass I mean not just a warranted conclusion that psychotherapy is or is not effective for such and such conditions—though that would be much—but a discriminating set of unrefuted propositions which would define attainable goals appropriate to categories of illness or of personality, classify forms of psychotherapy in terms that could be applied without ambiguity to the practice of any psychiatrist, and provide a more "objective", more public and uncontaminated analysis of the therapeutic process than any now offered.

These may seem overweening hopes, in the light of what we have had for so long. but, even if they were fulfilled it would still be only an instalment, largely empirical, of what is needed to free psychotherapy from clogging uncertainties. Current methods of psychological treatment are, or seem to be, legion, they doubtless include procedures that can do harm, at any rate in irresponsible hands, and for some of them the connection between theory and practice is tenuous, the connection between what is preached and what is done so remote as to be discreditable. Besides these infirmities, there is of course much strength and much achievement. How could it be otherwise when there are so many psychiatrists of great ability and intellectual integrity, broadly trained, and gifted in handling complex relationships with others, who devote themselves without reservation or misgiving to psychotherapy as their main business in life? It is in no sense derogatory of their work to want psychological treatment put on a firmer basis of confirmation and precision than it now has. A fair-minded and illuminating review of psychotherapy in 1955 included the following declaration:

> "In our present ignorance it is practically certain that clients are treated by methods of varying inappropriateness, largely as a function of which therapist they happen to get to. Also it is practically certain that many hours of skilled therapists are being spent with unmodifiable cases, or in the use of techniques which are effective but unnecessarily time-consuming" (Meehl 1955).

This is true, and it has a moral—a moral that can be drawn with special force in a Welfare State like ours, under obligation to provide its citizens with all the approved medical treatment they need. To withhold psychotherapy from any neurotic invalid, or any delinquent, or anyone with psychopathic personality—once it had been demonstrated properly that such treatment would lead to recovery or much improvement in these people—would be indefensible. It would be indefensible, within a comprehensive national health service, even if elaborate treatment were shown to be requisite for many patients. practical objections would be raised, of course, on grounds of cost and the availability of doctors, but the issue turns essentially on whether there is convincing evidence of the value of treatment. The United States Department of Health recently published a book on *Evaluation in Mental Health* which listed and abstracted 980 relevant articles. It concluded " an obvious finding is the thinness of the efforts at evaluation."

Here, then, is a great domain of psychiatric practice in which there has been an excessive proportion of guesswork and rather a lot of subjective certainty. More doubt might have been salutary, for the reason that Bacon stated "if a man will begin with certainties, he shall end in doubts, but if he will be content to begin with doubts, he shall end in certainties." The remedy lies in the hands of psychiatrists and psychologists working together. It will demand a considerable effort of reorientation, and indeed sacrifices, from those psychiatrists who devote most of their time to systematic psychotherapy, and from psychologists it will demand an intimate understanding of the conditions of clinical practice and, indeed, some reorientation likewise.

(*to be concluded*)

LEUKÆMIA AND RELATED CONDITIONS AND THE BLOOD-URIC-ACID

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GOUT develops very rarely in typical myeloid leukæmia and rarely in typical polycythæmia, but not uncommonly in atypical cases of both these diseases, particularly cases of leukæmia without the very high leucocyte-count (100,000 per c.cm.) in the circulating blood of typical cases, and cases of polycythæmia in which a high leucocyte-count occurs in the circulating blood in addition to the high erythrocyte-count (Hickling 1953). It is in such cases that myeloid metaplasia involving leucoblasts, erythroblasts, and especially megakaryocytes develops.

The association of gout with this type of myeloid metaplasia seems important, and, since a patient may have a high blood-uric-acid level for years without any sign of gout, the present paper is concerned with observations on the blood-uric-acid levels of patients with myeloid metaplasia of the spleen, including some cases of typical myeloid leukæmia, the blood-uric-acid levels being related to the histological changes found in bone-marrow and spleen.

It has been found that there is a very close association between a high blood-uric-acid level and the presence of large numbers of giant cells, closely resembling megakaryocytes, in the bone-marrow and in the tissues affected by myeloid metaplasia. This particular association is the reason why gout is very rare in typical myeloid leukæmia, the cells in the tissues and bone-marrow being chiefly leucoblasts, and why gout occurs more commonly in polycythæmia, in which it has been known for many years that myeloid metaplasia may involve leucoblasts and megakaryocytes in addition to the erythroblasts (Weber 1921).

The relationship between a high blood-uric-acid level and megakaryocyte-like giant cells in the bone-marrow and in the tissues affected by myeloid metaplasia appears to be a reciprocal one, because, when a leukæmia-like disease develops in a patient who has had gout for years, it is an atypical leukæmia, often an " erythroleukæmia ", the leucocytes not reaching " leukæmic " numbers, and the tissue changes are those of " megakaryocytic myelosis ", sometimes with sclerosis of the bone-marrow in addition to large numbers of megakaryocyte-like giant cells. This is of great importance in considering the ætiology of leukæmia, because very few conditions are known to cause myeloid metaplasia, the essential feature of myeloid leukæmia.

Observations

These statements are based upon observations of the blood-uric-acid levels in 58 patients, who have as common factors massive myeloid splenomegaly, with various associated changes in the circulating blood, the most important of which is the presence of immature leucocytes. The number of leucocytes in the circulating blood and the percentage of immature cells vary very greatly through the series, from the typical cases of myeloid leukæmia, with more than 100,000 per c.mm. and a considerable proportion of immature cells, to the leucopenia, with a very low proportion of immature cells, of a few cases of " megakaryocytic myelosis ", polycythæmia, or osteo- or myelo-sclerosis. But the detection of immature red and white cells in the circulating blood is of very great importance in the diagnosis of myeloid splenomegaly, and other signs of this may be basophilia, sometimes very high, and eosinophilia.

The 58 cases may be classified as follows:

13 cases of myeloid leukæmia with typical circulating blood, in 5 of which histological findings are available.

4 cases of myeloid leukæmia in which, before treatment, the leucocytes did not reach " leukæmic " numbers (about 100,000 per c.mm.), histological findings are available in 2 of them.

10 cases of polycythæmia, in 8 of which histological findings are available.

11 cases of osteosclerosis, with distinct radiological changes in the bones, in 10 of which histological findings are available.

11 cases of myelosclerosis, in all of which histological findings are available.

6 cases of " megakaryocytic myelosis," in all of which histological findings are available.

3 cases of chronic non-leukæmic myeloid splenomegaly (Witts 1956), in all of which histological findings are available.

These divisions are made for convenience only, and many cases could be put into other divisions. For example, 1 patient with myeloid leukæmia had considerable megakaryocyte proliferation in the bone-marrow, all the patients with polycythæmia had well-marked megakaryocytic proliferation in the bone-marrow or in the tissues, or in both, 2 of the patients with megakaryocytic myelosis had some very fine sclerosis of the bone-marrow, and several patients with osteosclerosis and with myelosclerosis had considerable megakaryocytic proliferation of the bone-marrow in addition to the sclerotic changes. The relationship between these cases is discussed later.

To save repetition, throughout the paper figures for blood-uric-acid levels indicate the number of milligrammes in 100 ml. of blood, the estimations being made on blood-serum. The term giant cells means giant cells closely resembling megakaryocytes, as these appear in sections of bone-marrow.

MYELOID LEUKÆMIA

Of the 13 patients with typical circulating blood 12 had uric-acid levels of 3 1–6 6 mg except for short periods at the beginning of X-ray treatment, when levels of 7 0–9 5 mg were found, the levels later returning to the previous values 5 patients died of myeloid leukæmia, but no histological findings were available In 5 cases histological findings were available, and the proliferation of the bone-marrow and the myeloid metaplasia of the tissues was predominantly leucoblastic without conspicuous giant cells 1 patient had a considerable increase in the reticulin fibres in the bone-marrow together with leucoblastic proliferation 2 patients are still living, with uric-acid levels of 3 4–5 6 mg

4 patients in this group did not have typical leukæmic circulating blood 1 of these had a uric-acid level of 4 0 mg with typical leucoblastic changes in the bone-marrow and typical leucoblastic myeloid metaplasia of the tissues 1 had uric-acid levels of 6 7–11 7 mg (seven estimations in a year) and conspicuous giant cells in the proliferated bone-marrow The 2 other patients had uric-acid levels of 10 0 mg and 9 1 mg , but no histological findings are available None of the patients with myeloid leukæmia had gout

POLYCYTHÆMIA

Of the 10 cases in this group 4 were seen in an early stage, when spleens were not massive, and when there was no leucocytosis and there were either no or very few immature leucocytes in the circulating blood The uric-acid level in all at this stage was 2 1–4 9 mg 1 patient died four years later, but no more uric-acid estimations were made 1 died nine years later and had many giant cells in a sclerotic bone-marrow and in the myeloid metaplasia of the spleen, but no further uric-acid levels were estimated In another patient, however, who is still living, the spleen has become much larger, small numbers of immature leucocytes are constantly present in the circulating blood, the blood-uric-acid level has risen to 7 9–12 0 mg , and bone-marrow biopsy shows a great many giant cells, with some very fine sclerosis The 4th patient, also still living after twelve years' observation, has developed massive splenomegaly, a high leucocytosis (up to 40,000 per c mm), and blood-uric-acid levels of 6 6–7 7 mg No histological findings are yet available

The remaining 6 patients with polycythæmia were seen when already they had massive splenomegaly, with leucocytosis and immature leucocytes in the circulating blood The blood-uric-acid levels in all of them were 6 6–13 3 mg , very often above 7 5 mg 1 patient died seven years after being seen (no histological findings), 1 is still living, in whom bone-marrow biopsy shows a great many giant cells, 1 died after seven years' observation and had a great many giant cells in the bone-marrow, no sclerosis, myeloid metaplasia of the spleen, and very slight myeloid metaplasia of the liver, 1 died after seven years' observation and had a great many giant cells in the bone-marrow, with slight sclerosis in places, 1 died after six years' observation and had a great many giant cells in the bone-marrow, and the last is still living, bone-marrow biopsy showing well-marked giant-cell proliferation, with early sclerosis 5 of the patients with polycythæmia had gout

OSTEOSCLEROSIS

Of the 11 patients in this group, 6 had blood-uric-acid levels of 6 6–12 0 mg constantly, with large numbers of giant cells in the osteomyelosclerotic bone-marrow and large numbers of giant cells in the myeloid metaplasia of the spleen 1 patient had uric-acid levels of 7 0–10 0 mg (eight estimations in two years) with no giant cells in the myeloid metaplasia of the liver or of the spleen (the bone-marrow was not examined) 3 patients had blood-uric-acid levels of 4 0–6 0 mg throughout the period of observation, and there were no conspicuous giant cells in the osteosclerotic bone-marrow or in the myeloid metaplasia of the spleen or of other tissues 1 had uric-acid levels of 5 4–6 6 mg , but the patient is still alive, and no histological findings are yet available 4 of the patients with osteosclerosis had gout

MYELOSCLEROSIS

There are 11 patients in this group In 5 the uric-acid levels were 6 1–7 7 mg (five estimations in a year), 5 7–8 3 mg (four estimations in two years), 7 5–10 7 mg (nine estimations in three years), 7 0–9 0 mg (eleven estimations in five years), and 8 0–10 4 mg (two estimations in four weeks), and all 5 had conspicuous giant cells in the bone-marrow and in the organs affected by myeloid metaplasia 5 had uric-acid levels of 2 8–5 3 mg and no giant cells in the bone-marrow or in the organs affected by myeloid metaplasia 1 patient had uric-acid levels of 2 0–5 8 mg over a period of six months and then 6 7–7 8 mg over the next nine months At necropsy he was found to have a great many giant cells in the bone-marrow, with very fine sclerosis and myeloid metaplasia of the spleen and the liver without conspicuous giant cells The last patient had myelosclerosis with large numbers of giant cells in the sclerotic bone-marrow associated with the presence of malignant cells from a malignant prostate in the bone-marrow He had myeloid metaplasia of the liver and the spleen His blood-uric-acid levels were 5 1–9 6 mg over a period of two years 2 of the patients with myelosclerosis had gout

MEGAKARYOCYTIC MYELOSIS

There are 6 patients in this group, 3 had gout, 2 after the splenomegaly and other features had been recognised, and 1 started to get attacks of gout twelve years before the splenomegaly was recognised 1 patient had uric-acid levels of 6 4–11 4 mg (twenty-one estimations in thirteen years), 1 had 12 5–16 mg over three months, and 1 had 7 8–11 2 mg (four estimations in a year) All 3 had a great many giant cells in the bone-marrow, 2 had localised masses of myeloid metaplasia in the spleen containing very large numbers of giant cells In another patient the uric-acid levels were 5 5–8 6 mg over five months, and he had large numbers of giant cells in the bone-marrow, with very fine sclerosis The remaining 2 patients were exceptions in 1 the uric-acid level was 7 0 mg or higher only five times out of nineteen estimations in six years, but the bone-marrow showed a great many giant cells with doubtful early sclerosis, with myeloid metaplasia of the spleen, and in 1 other patient there was a single estimation of blood-uric-acid (4 5 mg), and bone-marrow biopsy two years later showed large numbers of giant cells with early sclerosis

CHRONIC NON-LEUKÆMIC MYELOID SPLENOMEGALY

3 cases are placed in this group because, though they had massive myeloid splenomegaly, the bone-marrow was normal, being neither hyperplastic nor sclerotic All died of weakness and wasting None had any prominent giant-cell proliferation in the myeloid metaplasia of the spleen or the liver 1, observed for seven years, had blood-uric-acid levels of 2 7–6 3 mg (eight estimations), 1, observed for two months, a uric-acid level of 5 7 mg , and 1, observed for three years, had uric-acid levels of 4 9, 6 7, and 8 0 mg

Throughout the study occasional blood-urea estimations were made (which were always found to be normal) to ensure that raised blood-uric-acid levels were not part of a general retention of nitrogen

Discussion

With few exceptions the blood-uric-acid levels of patients with myeloid leukæmia and related conditions, without conspicuous giant cells in the bone-marrow or in the organs affected by myeloid metaplasia, were between 2 1 and 6 6 mg and of patients with conspicuous giant cells, also with few exceptions, between 6 6 and 12 0 mg These observations suggest that blood-uric-acid levels in myeloid splenomegaly are an important guide to the type of myeloid metaplasia present, and may enable a gradual change in the type of histological change in the bone-marrow and organs affected by myeloid metaplasia to be recognised

A study of cases of myeloid splenomegaly, some of them for many years, suggests certain conclusions

Probably as a result of a metabolic disorder, bone-marrow cells proliferate and blood-cells are formed in the spleen and elsewhere This earliest stage is very rarely seen because it is usually symptomless, but it may occasionally be found in routine examinations, when slight enlargement of the spleen and increase in red cells, white cells, and platelets and slight basophilia in the circulating blood are found, or this stage may be found in the investigation of abnormal hæmorrhage—e g , into the tissues—or in the investigation of gout. There is no information about whether ordinary cases of myeloid leukæmia pass through such a stage, because the known histology of that disorder is the histology revealed at necropsy, but the fact that a few patients with myeloid leukæmia have a raised blood-uric-acid level suggests that there may be a stage of general blood-cell proliferation before the mainly leucoblastic proliferation is established When first seen, most patients have already massive splenomegaly and 100,000 leucocytes or more per c mm in the circulating blood, suggesting that the disorder has been long established before symptoms are sufficiently severe to cause the patient to seek advice.

The first stage, of general proliferation of bone-marrow cells and myeloid metaplasia of the spleen, may be followed by a stage of chiefly red-cell proliferation, when the symptoms and signs of polycythæmia may be produced, and by a stage of chiefly megakaryocyte proliferation, and this by a stage with increasing reticulin proliferation, followed by marrow sclerosis and then by calcification and osteosclerosis The blood-uric-acid level is a guide in tracing these stages, because megakaryocytes in large numbers may persist into the myelosclerotic and osteosclerotic stages or they may be obliterated It is doubtful if myelosclerosis and osteosclerosis occur without a preceding stage with megakaryocyte proliferation. Each of these stages may last many years, and there is no correlation between the underlying pathological state of the bone-marrow and myeloid metaplasia and the clinical and hæmatological features, and this has caused much confusion The best-known types are the chronic cases of megakaryocytic myelosis, myelosclerosis, and osteosclerosis the patients live for years with little interference with their general health, the commonest symptoms being those due to the splenomegaly, and death is ultimately due to weakness, wasting, and anæmia But acute and subacute cases occur in all three stages The acute cases have a course exactly similar to that of acute leukæmia, the patient having pyrexia, severe anæmia, and hæmorrhages and dying in a few weeks or months Even patients with very dense osteosclerosis or myelosclerosis, which probably took many years to develop, may have no symptoms until they manifest an acute illness exactly like acute leukæmia There were 3 acute cases in this series 1 of early myelosclerosis, 1 of dense advanced myelosclerosis, and 1 of dense osteosclerosis Several acute cases have been described (Assmann 1907, Firket and Campos 1922) Subacute cases are those which are seen because of anæmia and weakness, and the patients remain weak and ill throughout the period of observation, unaffected by treatment except temporarily by blood-transfusion There were 6 subacute cases in this series, all of which presented various degrees of osteosclerosis or myelosclerosis, some with and some without conspicuous giant cells among the fibrous tissue Several subacute cases have been described (Wood and Andrews 1949)

Just as there is no correlation between the type of histological change in bone-marrow and spleen and the clinical condition of the patient, there is also no correlation with the state of the circulating blood In a patient with megakaryocytic myelosis, myelosclerosis, or osteosclerosis the numbers of red cells, leucocytes, and platelets may be high, normal, or low, there being very great variations from case to case, and the blood picture may change greatly under observation The great variations in the circulating blood and in the histological picture have been well described (Hutt et al 1953, Richmond and Duncan 1956, Korst et al 1956)

Korst et al (1956) found raised blood-uric-acid levels in 6 of their 23 patients with "myelofibrosis" but did not correlate this finding with histological changes A patient with anæmia may develop polycythæmia (Hutt and Richardson 1950), a patient with polycythæmia may develop "leucoerythroblastic anæmia" (Stone and Woodman 1938), a patient with "leucoerythroblastic anæmia" may develop polycythæmia (Schwarz 1939), a patient with "leukæmic" blood may develop polycythæmia (Major and Weber 1943), and patients may have a blood picture both "leukæmic" and "polycythæmic" (McAlpin 1929, Klumpp and Hertig 1932, Meulengracht and Petri 1932)

6 patients had gout for years before splenomegaly was first discovered because of abdominal symptoms or during the investigation of weakness, cramps in the legs at night, or gout The intervals between the first attack of gout and the discovery of splenomegaly in these 6 cases were three, six, seven, ten, twelve, and forty-one years Only 1 patient was seen before the discovery of splenomegaly gout started in 1929, and he was seen in 1930 because of a large hæmorrhage from the bowel, but the spleen was not felt then, abdominal symptoms, leading to the discovery of a large spleen, developed in 1936 3 of these 6 patients are in the polycythæmia group, 2 in the myelosclerosis group (one very early sclerosis, the other advanced sclerosis), and 1 in the megakaryocytic myelosis group 5 had very large numbers of giant cells in the bone-marrow, and 1 very large numbers in the spleen, with dense bone-marrow sclerosis

If the numbers of leucocytes in the circulating blood in the chronic cases are considerably increased—e g , 30,000 per c.mm —a good response to X-irradiation of the spleen or to busulphan by mouth may be obtained regardless of the type of underlying histology The spleen becomes smaller, the weakness improves, and cramps in the legs disappear Good response to X-ray treatment was obtained in 3 cases of polycythæmia, 3 cases of osteosclerosis, 2 cases of myelosclerosis, and 1 case of megakaryocytic myelosis, and to busulphan in 5 cases, all of which had been treated with at least one course of X rays As with ordinary leukæmia, the effect of treatment lasts a variable length of time, and subsequent courses of treatment tend to have diminishingly good results As opposed to ordinary leukæmia, most patients with a chronic illness die of weakness, wasting, and anæmia, and sometimes chronic gout, without an acute "leukæmic" termination Only 1 chronic case in the series, with dense osteosclerosis, presented a terminal blood picture like that of an ordinary case of myeloid leukæmia with very large numbers of myeloblasts

In only 2 instances in this series was there very evident phagocytosis by the giant cells There was no correlation between large numbers of giant cells in the tissues and large numbers of platelets in the circulating blood Almost always, however, giant platelets were found, and in most cases a few megakaryocytes were, at times, found in the circulating blood These may occur, however, in typical

MYELOID LEUKÆMIA

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4 patients in this group did not have typical leukæmic circulating blood 1 of these had a uric-acid level of 4 0 mg with typical leucoblastic changes in the bone-marrow and typical leucoblastic myeloid metaplasia of the tissues 1 had uric-acid levels of 6 7–11 7 mg (seven estimations in a year) and conspicuous giant cells in the proliferated bone-marrow The 2 other patients had uric-acid levels of 10 0 mg and 9 1 mg , but no histological findings are available None of the patients with myeloid leukæmia had gout

POLYCYTHÆMIA

Of the 10 cases in this group 4 were seen in an early stage, when spleens were not massive, and when there was no leucocytosis and there were either no or very few immature leucocytes in the circulating blood The uric-acid level in all at this stage was 2 1–4 9 mg 1 patient died four years later, but no more uric-acid estimations were made 1 died nine years later and had many giant cells in a sclerotic bone-marrow and in the myeloid metaplasia of the spleen, but no further uric-acid levels were estimated In another patient, however, who is still living, the spleen has become much larger, small numbers of immature leucocytes are constantly present in the circulating blood, the blood-uric-acid level has risen to 7 9–12 0 mg , and bone-marrow biopsy shows a great many giant cells, with some very fine sclerosis The 4th patient, also still living after twelve years' observation, has developed massive splenomegaly, a high leucocytosis (up to 40,000 per c mm), and blood-uric-acid levels of 6 6–7 7 mg No histological findings are yet available

The remaining 6 patients with polycythæmia were seen when already they had massive splenomegaly, with leucocytosis and immature leucocytes in the circulating blood The blood-uric-acid levels in all of them were 6 6–13 3 mg , very often above 7 5 mg 1 patient died seven years after being seen (no histological findings), 1 is still living, in whom bone-marrow biopsy shows a great many giant cells, 1 died after seven years' observation and had a great many giant cells in the bone-marrow, no sclerosis, myeloid metaplasia of the spleen, and very slight myeloid metaplasia of the liver, 1 died after seven years' observation and had a great many giant cells in the bone-marrow, with slight sclerosis in places, 1 died after six years' observation and had a great many giant cells in the bone-marrow, and the last is still living, bone-marrow biopsy showing well-marked giant-cell proliferation, with early sclerosis 5 of the patients with polycythæmia had gout

OSTEOSCLEROSIS

Of the 11 patients in this group, 6 had blood-uric-acid levels of 6 6–12 0 mg constantly, with large numbers of giant cells in the osteomyelosclerotic bone-marrow and large numbers of giant cells in the myeloid metaplasia of the spleen 1 patient had uric-acid levels of 7 0–10 0 mg (eight estimations in two years) with no giant cells in the myeloid metaplasia of the liver or of the spleen (the bone-marrow was not examined) 3 patients had blood-uric-acid levels of 4 0–6 0 mg throughout the period of observation, and there were no conspicuous giant cells in the osteosclerotic bone-marrow or in the myeloid metaplasia of the spleen or of other tissues 1 had uric-acid levels of 5 4–6 6 mg , but the patient is still alive, and no histological findings are yet available 4 of the patients with osteosclerosis had gout

MYELOSCLEROSIS

There are 11 patients in this group In 5 the uric-acid levels were 6 1–7 7 mg (five estimations in a year), 5 7–8 3 mg (four estimations in two years), 7 5–10 7 mg (nine estimations in three years), 7 0–9 0 mg (eleven estimations in five years), and 8 0–10 4 mg (two estimations in four weeks), and all 5 had conspicuous giant cells in the bone-marrow and in the organs affected by myeloid metaplasia 5 had uric-acid levels of 2 8–5 3 mg and no giant cells in the bone-marrow or in the organs affected by myeloid metaplasia 1 patient had uric-acid levels of 2 0–5 8 mg over a period of six months and then 6 7–7 8 mg over the next nine months At necropsy he was found to have a great many giant cells in the bone-marrow, with very fine sclerosis and myeloid metaplasia of the spleen and the liver without conspicuous giant cells The last patient had myelosclerosis with large numbers of giant cells in the sclerotic bone-marrow associated with the presence of malignant cells from a malignant prostate in the bone-marrow He had myeloid metaplasia of the liver and the spleen His blood-uric-acid levels were 5 1–9 6 mg over a period of two years 2 of the patients with myelosclerosis had gout

MEGAKARYOCYTIC MYELOSIS

There are 6 patients in this group, 3 had gout, 2 after the splenomegaly and other features had been recognised, and 1 started to get attacks of gout twelve years before the splenomegaly was recognised 1 patient had uric-acid levels of 6 4–11 4 mg (twenty-one estimations in thirteen years), 1 had 12 5–16 mg over three months, and 1 had 7 8–11 2 mg (four estimations in a year) All 3 had a great many giant cells in the bone-marrow, 2 had localised masses of myeloid metaplasia in the spleen containing very large numbers of giant cells In another patient the uric-acid levels were 5 5–8 6 mg over five months, and he had large numbers of giant cells in the bone-marrow, with very fine sclerosis The remaining 2 patients were exceptions in 1 the uric-acid level was 7 0 mg or higher only five times out of nineteen estimations in six years, but the bone-marrow showed a great many giant cells with doubtful early sclerosis, with myeloid metaplasia of the spleen, and in 1 other patient there was a single estimation of blood-uric-acid (4 5 mg), and bone-marrow biopsy two years later showed large numbers of giant cells with early sclerosis

CHRONIC NON-LEUKÆMIC MYELOID SPLENOMEGALY

3 cases are placed in this group because, though they had massive myeloid splenomegaly, the bone-marrow was normal, being neither hyperplastic nor sclerotic All died of weakness and wasting None had any prominent giant-cell proliferation in the myeloid metaplasia of the spleen or the liver 1, observed for seven years, had blood-uric-acid levels of 2 7–6 3 mg (eight estimations), 1, observed for two months, a uric-acid level of 5 7 mg , and 1, observed for three years, had uric-acid levels of 4 9, 6 7, and 8 0 mg

Throughout the study occasional blood-urea estimations were made (which were always found to be normal) to ensure that raised blood-uric-acid levels were not part of a general retention of nitrogen

Discussion

With few exceptions the blood-uric-acid levels of patients with myeloid leukæmia and related conditions, without conspicuous giant cells in the bone-marrow or in the organs affected by myeloid metaplasia, were between 2 1 and 6 6 mg and of patients with conspicuous giant cells, also with few exceptions, between 6 6 and 12 0 mg These observations suggest that blood-uric-acid levels in myeloid splenomegaly are an important guide to the type of myeloid metaplasia present, and may enable a gradual change in the type of histological change in the bone-marrow and organs affected by myeloid metaplasia to be recognised

A study of cases of myeloid splenomegaly, some of them for many years, suggests certain conclusions

Probably as a result of a metabolic disorder, bone-marrow cells proliferate and blood-cells are formed in the spleen and elsewhere This earliest stage is very rarely seen because it is usually symptomless, but it may occasionally be found in routine examinations, when slight enlargement of the spleen and increase in red cells, white cells, and platelets and slight basophilia in the circulating blood are found, or this stage may be found in the investigation of abnormal hæmorrhage—e g , into the tissues—or in the investigation of gout. There is no information about whether ordinary cases of myeloid leukæmia pass through such a stage, because the known histology of that disorder is the histology revealed at necropsy, but the fact that a few patients with myeloid leukæmia have a raised blood-uric-acid level suggests that there may be a stage of general blood-cell proliferation before the mainly leucoblastic proliferation is established When first seen, most patients have already massive splenomegaly and 100,000 leucocytes or more per c.mm in the circulating blood, suggesting that the disorder has been long established before symptoms are sufficiently severe to cause the patient to seek advice.

The first stage, of general proliferation of bone-marrow cells and myeloid metaplasia of the spleen, may be followed by a stage of chiefly red-cell proliferation, when the symptoms and signs of polycythæmia may be produced, and by a stage of chiefly megakaryocyte proliferation, and this by a stage with increasing reticulin proliferation, followed by marrow sclerosis and then by calcification and osteosclerosis The blood-uric-acid level is a guide in tracing these stages, because megakaryocytes in large numbers may persist into the myelosclerotic and osteosclerotic stages or they may be obliterated It is doubtful if myelosclerosis and osteosclerosis occur without a preceding stage with megakaryocyte proliferation Each of these stages may last many years, and there is no correlation between the underlying pathological state of the bone-marrow and myeloid metaplasia and the clinical and hæmatological features, and this has caused much confusion The best-known types are the chronic cases of megakaryocytic myelosis, myelosclerosis, and osteosclerosis the patients live for years with little interference with their general health, the commonest symptoms being those due to the splenomegaly, and death is ultimately due to weakness, wasting, and anæmia. But acute and subacute cases occur in all three stages The acute cases have a course exactly similar to that of acute leukæmia, the patient having pyrexia, severe anæmia, and hæmorrhages and dying in a few weeks or months Even patients with very dense osteosclerosis or myelosclerosis, which probably took many years to develop, may have no symptoms until they manifest an acute illness exactly like acute leukæmia. There were 3 acute cases in this series 1 of early myelosclerosis, 1 of dense advanced myelosclerosis, and 1 of dense osteosclerosis Several acute cases have been described (Assmann 1907, Firket and Campos 1922) Subacute cases are those which are seen because of anæmia and weakness, and the patients remain weak and ill throughout the period of observation, unaffected by treatment except temporarily by blood-transfusion There were 6 subacute cases in this series, all of which presented various degrees of osteosclerosis or myelosclerosis, some with and some without conspicuous giant cells among the fibrous tissue Several subacute cases have been described (Wood and Andrews 1940)

Just as there is no correlation between the type of histological change in bone-marrow and spleen and the clinical condition of the patient, there is also no correlation with the state of the circulating blood In a patient with megakaryocytic myelosis, myelosclerosis, or osteosclerosis the numbers of red cells, leucocytes, and platelets may be high, normal, or low, there being very great variations from case to case, and the blood picture may change greatly under observation The great variations in the circulating blood and in the histological picture have been well described (Hutt et al 1953, Richmond and Duncan 1956, Korst et al 1956)

Korst et al (1956) found raised blood-uric-acid levels in 6 of their 23 patients with " myelofibrosis " but did not correlate this finding with histological changes A patient with anæmia may develop polycythæmia (Hutt and Richardson 1950), a patient with polycythæmia may develop " leucoerythroblastic anæmia " (Stone and Woodman 1938), a patient with " leucoerythroblastic anæmia " may develop polycythæmia (Schwarz 1939), a patient with " leukæmic " blood may develop polycythæmia (Major and Weber 1943), and patients may have a blood picture both " leukæmic " and " polycythæmic " (McAlpin 1929, Klumpp and Hertig 1932, Meulengracht and Petri 1932)

6 patients had gout for years before splenomegaly was first discovered because of abdominal symptoms or during the investigation of weakness, cramps in the legs at night, or gout. The intervals between the first attack of gout and the discovery of splenomegaly in these 6 cases were three, six, seven, ten, twelve, and forty-one years Only 1 patient was seen before the discovery of splenomegaly gout started in 1929, and he was seen in 1930 because of a large hæmorrhage from the bowel, but the spleen was not felt then, abdominal symptoms, leading to the discovery of a large spleen, developed in 1936 3 of these 6 patients are in the polycythæmia group, 2 in the myelosclerosis group (one very early sclerosis, the other advanced sclerosis), and 1 in the megakaryocytic myelosis group 5 had very large numbers of giant cells in the bone-marrow, and 1 very large numbers in the spleen, with dense bone-marrow sclerosis

If the numbers of leucocytes in the circulating blood in the chronic cases are considerably increased—e g , 30,000 per c.mm —a good response to X-irradiation of the spleen or to busulphan by mouth may be obtained regardless of the type of underlying histology The spleen becomes smaller, the weakness improves, and cramps in the legs disappear Good response to X-ray treatment was obtained in 3 cases of polycythæmia, 3 cases of osteosclerosis, 2 cases of myelosclerosis, and 1 case of megakaryocytic myelosis, and to busulphan in 5 cases, all of which had been treated with at least one course of X rays As with ordinary leukæmia, the effect of treatment lasts a variable length of time, and subsequent courses of treatment tend to have diminishingly good results As opposed to ordinary leukæmia, most patients with a chronic illness die of weakness, wasting, and anæmia, and sometimes chronic gout, without an acute " leukæmic " termination Only 1 chronic case in the series, with dense osteosclerosis, presented a terminal blood picture like that of an ordinary case of myeloid leukæmia with very large numbers of myeloblasts

In only 2 instances in this series was there very evident phagocytosis by the giant cells There was no correlation between large numbers of giant cells in the tissues and large numbers of platelets in the circulating blood Almost always, however, giant platelets were found, and in most cases a few megakaryocytes were, at times, found in the circulating blood These may occur, however, in typical

MYELOID LEUKÆMIA

Of the 13 patients with typical circulating blood 12 had uric-acid levels of 3 1–6 6 mg except for short periods at the beginning of X-ray treatment, when levels of 7 0–9 5 mg were found, the levels later returning to the previous values 5 patients died of myeloid leukæmia, but no histological findings were available In 5 cases histological findings were available, and the proliferation of the bone-marrow and the myeloid metaplasia of the tissues was predominantly leucoblastic without conspicuous giant cells 1 patient had a considerable increase in the reticulin fibres in the bone-marrow together with leucoblastic proliferation 2 patients are still living, with uric-acid levels of 3 4–5 6 mg

4 patients in this group did not have typical leukæmic circulating blood 1 of these had a uric-acid level of 4 0 mg with typical leucoblastic changes in the bone-marrow and typical leucoblastic myeloid metaplasia of the tissues 1 had uric-acid levels of 6 7–11 7 mg (seven estimations in a year) and conspicuous giant cells in the proliferated bone-marrow The 2 other patients had uric-acid levels of 10 0 mg and 9 1 mg, but no histological findings are available None of the patients with myeloid leukæmia had gout

POLYCYTHÆMIA

Of the 10 cases in this group 4 were seen in an early stage, when spleens were not massive, and when there was no leucocytosis and there were either no or very few immature leucocytes in the circulating blood The uric-acid level in all at this stage was 2 1–4 9 mg 1 patient died four years later, but no more uric-acid estimations were made 1 died nine years later and had many giant cells in a sclerotic bone-marrow and in the myeloid metaplasia of the spleen, but no further uric-acid levels were estimated In another patient, however, who is still living, the spleen has become much larger, small numbers of immature leucocytes are constantly present in the circulating blood, the blood-uric-acid level has risen to 7 9–12 0 mg, and bone-marrow biopsy shows a great many giant cells, with some very fine sclerosis The 4th patient, also still living after twelve years' observation, has developed massive splenomegaly, a high leucocytosis (up to 40,000 per c mm), and blood-uric-acid levels of 6 6–7 7 mg No histological findings are yet available

The remaining 6 patients with polycythæmia were seen when already they had massive splenomegaly, with leucocytosis and immature leucocytes in the circulating blood The blood-uric-acid levels in all of them were 6 6–13 3 mg, very often above 7 5 mg 1 patient died seven years after being seen (no histological findings), 1 is still living, in whom bone-marrow biopsy shows a great many giant cells, 1 died after seven years' observation and had a great many giant cells in the bone-marrow, no sclerosis, myeloid metaplasia of the spleen, and very slight myeloid metaplasia of the liver, 1 died after seven years' observation and had a great many giant cells in the bone-marrow, with slight sclerosis in places, 1 died after six years' observation and had a great many giant cells in the bone-marrow, and the last is still living, bone-marrow biopsy showing well-marked giant-cell proliferation, with early sclerosis 5 of the patients with polycythæmia had gout

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Of the 11 patients in this group, 6 had blood-uric-acid levels of 6 6–12 0 mg constantly, with large numbers of giant cells in the osteomyelosclerotic bone-marrow and large numbers of giant cells in the myeloid metaplasia of the spleen 1 patient had uric-acid levels of 7 0–10 0 mg (eight estimations in two years) with no giant cells in the myeloid metaplasia of the liver or of the spleen (the bone-marrow was not examined) 3 patients had blood-uric-acid levels of 4 0–6 0 mg throughout the period of observation, and there were no conspicuous giant cells in the osteosclerotic bone-marrow or in the myeloid metaplasia of the spleen or of other tissues 1 had uric-acid levels of 5 4–6 6 mg, but the patient is still alive, and no histological findings are yet available 4 of the patients with osteosclerosis had gout

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With few exceptions the blood-uric-acid levels of patients with myeloid leukæmia and related conditions, without conspicuous giant cells in the bone-marrow or in the organs affected by myeloid metaplasia, were between 2 1 and 6 6 mg and of patients with conspicuous giant cells, also with few exceptions, between 6 6 and 12 0 mg These observations suggest that blood-uric-acid levels in myeloid splenomegaly are an important guide to the type of myeloid metaplasia present, and may enable a gradual change in the type of histological change in the bone-marrow and organs affected by myeloid metaplasia to be recognised

A study of cases of myeloid splenomegaly, some of them for many years, suggests certain conclusions

TABLE I—AGE OF PATIENTS

Group	Age (yr)				
	0–20	21–30	31–40	40–50	Total
S	67	653	281	18	1019
S—	60	643	273	24	1000

records were given to the investigator at the end of the puerperium

As soon as the first 200 women had been delivered, the number of toxæmias in both groups were assessed There were 8 in group S, and 12 in group S— Each group contained 100 women It was decided that it was safe to continue the investigation

Results

The investigation started in August, 1954 By August, 1956, 2077 patients had begun treatment, and the last delivery was in April, 1957

Of these, 1039 had been told to take more salt 7 of them left the borough before delivery, 10 miscarried, and 3 were later found not to be pregnant Therefore 20 cases had to be discarded, leaving 1019 completed cases

TABLE II—PARITY OF PATIENTS

Group	Parity			
	0	1–3	4 or more	Total
S	144	720	155	1019
S—	146	695	159	1000

1038 other women had been told to take less salt 10 of them left the borough before delivery, 22 miscarried, and 6 were found later not to be pregnant Therefore 38 had to be discarded, leaving 1000 completed cases

The women in both groups were more or less similar in age (table I), parity (table II), and time of first attendance at the clinics (table III)

There were 38 cases of toxæmia in the 1019 patients in group S and 97 in the 1000 patients in group S— The number of toxæmias is shown in relation to parity in table IV and to the mother's age in table V The toxæmias were fewer in group S at all ages and parities Table VI shows the toxæmias in detail in both groups One patient in group S— had gross œdema of legs, hands, face, and abdomen, with headaches and vomiting

All the other patients who had had œdema were then collected, those with varicose veins being discarded The numbers of cases with œdema alone were 163 in group S, and 287 in group S— Œdema of the legs alone was present in 121 patients in group S and 206 patients in group S— Œdema of the hands, abdomen, and legs was present in 42 patients in group S and 81 patients in group S—

TABLE III—DATES OF FIRST ATTENDANCE

Group	First attendance at (wks)			
	0–20	21–30	31–40	Total
S	531	384	104	1019
S—	518	346	136	1000

Table VII shows the numbers of patients in both groups who had had toxæmia in a previous pregnancy, together with details of those who developed toxæmia again in their present pregnancy In group S there were 40 such patients, of whom 5 again developed toxæmia, and in group S— there were 39 such patients, of whom 13 again developed toxæmia

All the other abnormal conditions present in both groups are shown in table VIII The incidence of œdema, perinatal deaths, antepartum hæmorrhage, and bleeding during pregnancy was lower in group S than in group S— Whereas the incidence of postpartum hæmorrhage, prematurity, deformities, and breech delivery was almost the same in both groups 2 of the 17 cases of antepartum hæmorrhage in group S were due to placenta prævia, and 15 were diagnosed as accidental hæmorrhage by the obstetricians in the hospital 4 of the 32 cases in group S— were due to placenta prævia, and 28 were diagnosed as accidental hæmorrhage by the obstetricians in hospital

TABLE IV—TOXÆMIA IN RELATION TO PARITY

—	Parity			
	0	1–3	4 or more	Total
Group S				
Patients	144	720	155	1019
Toxæmias	16	18	4	38
Group S—				
Patients	146	695	159	1000
Toxæmias	38	51	8	97

The numbers of premature births in both groups were almost the same, and the range of birthweights was similar However, the maturity by dates was not the same, because 21 infants were born at less than thirty-four weeks, with 13 perinatal deaths, in group S—, and only 11 infants at less than thirty-four weeks, with 4 perinatal deaths, in group S

Table IX shows the stillbirths in detail The deformities were anencephalus, hydrocephalus and spina bifida, exomphalos, and fœtus papyraceus The perinatal deaths are the stillbirths plus the deaths of infants in the first week of life , they were fewer in group S than in group S— The neonatal deaths are deaths in the first twenty-eight days after birth, they are given in detail in table X The neonatal deaths were fewer in group S than in group S— The greatest difference lay in the respiratory syndrome, which was variously described in the necropsy reports as atelectasis, vernix membrane, hæmorrhagic pneumonia, and cold injury

TABLE V—TOXÆMIA IN RELATION TO MOTHER'S AGE

—	Mother's age (yr)				
	0–20	21–30	31–40	41–50	Total
Group S					
Patients	67	653	281	18	1019
Toxæmias	4	20	12	2	38
Group S—					
Patients	60	643	273	24	1000
Toxæmias	10	54	28	5	97

During part of the investigation the placentas were weighed in 348 consecutive labours 176 placentas came from group S and 172 from group S— Twins were born to 6 women in group S and to 2 in group S— The twin placentas were discarded, leaving 170 placentas of single infants in each group The mean placental weight was 21 48 oz in group S and 20 90 oz in group S— Placental infarcts were found in 13 placentas in group S and in 32 placentas in group S—

TABLE VI—DETAILS OF TOXÆMIAS

Group	No	Raised B P	Alb	Raised B P Alb	Raised B P Œdema	Alb Œdema	Raised B P Alb Œdema	Severe œdema
S	38	9	0	4	9	0	16	0
S—	97	13	1	7	37	1	37	1

cases of myeloid leukæmia (Minot 1922) For example, in the cases of polycythæmia, platelets in the circulating blood were found to be very numerous in only 3 cases, and in the cases of megakaryocytic myelosis they were only very numerous constantly in 1 patient, being normal in number in the others In the cases of osteosclerosis and myelosclerosis in which large numbers of giant cells were present in the tissues, though the platelets in the circulating blood varied from time to time they were mostly normal or somewhat fewer than usual

The giant cells were studied (Goldschmid and Isaac 1922), and the conclusion was reached that they are phagocytic and also formed platelets Needle-puncture aspiration of bone-marrow is an unsatisfactory method of examination in this type of case The megakaryocytes seem to be very fragile and often appear in groups, so they may miss being aspirated in any particular puncture This has been repeatedly proved in the present series, where only on very few occasions were large numbers of megakaryocytes present in a bone-marrow aspirate, though biopsy showed conspicuous giant-cell proliferation

Summary

An account is given of the blood-uric-acid levels of 58 patients with myeloid splenomegaly—17 with myeloid leukæmia, 10 with polycythæmia, and the remaining 31 with myeloid splenomegaly associated with osteosclerosis, myelosclerosis, megakaryocytic myelosis, and similar conditions

A high blood-uric-acid level was very closely associated with the presence of large numbers of megakaryocyte-like giant cells in the bone-marrow and spleen

Blood-uric acid levels may be used as a guide to the type of myeloid metaplasia present, and the gradual change between some of the conditions mentioned above —e g, from polycythæmia to megakaryocytic myelosis, and from megakaryocytic myelosis to myelosclerosis—may be followed by determining the blood-uric-acid levels

When a leukæmia-like disorder appears in a patient who has had gout for years, the histological changes in the bone-marrow and spleen are those of megakaryocytic myelosis

Prof J Patterson and his chief assistant Dr J Swale, of Charing Cross Hospital Medical School, were responsible for practically every blood-uric-acid estimation Most of the patients on whom these observations were made were under my own care at Charing Cross Hospital Dr E C Warner, Dr N S Plummer, Dr P B S Fowler, of Charing Cross Hospital, Sir Alun Rowlands, and Dr John Ellis, of the London Hospital, and Dr W A Bourne and Dr E C B Keat, of the Royal Sussex County Hospital, Brighton, kindly allowed me to study cases under their care I am most grateful to all for their help

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SALT IN PREGNANCY

MARGARET ROBINSON
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SENIOR ASSISTANT MEDICAL OFFICER, DERBY

IN pregnant rats the appetite for sodium chloride increases more than the appetite for calcium (Richter and Barelare 1938) In 1945, on the suggestion of Prof F G Young, and under the auspices of the *Medical* Research Council, the effect of salt on the cramps of pregnancy in women was investigated in St Thomas's Hospital, London The results *were published by* Robinson (1947) The conclusion was that salt cured the cramps of pregnancy in a large percentage of cases, and that there was little risk of producing toxæmia of pregnancy by giving salt to cure the cramps of pregnancy

At a later date 915 pregnant women with cramps were treated, and there was *no greater incidence of toxæmia* among them than among 2690 untreated women attending the antenatal clinics during the same period It was found, however, that most of the *patients who complained of* severe cramp also disliked salt This dislike of salt made it difficult to persuade all of them to take enough additional salt to cure their cramps

It was decided that it would be better to prevent the cramps, if possible, by getting women to take more salt early in pregnancy, but before doing this it was essential to find out whether extra salt in the diet of pregnant women did or did not increase the incidence of toxæmia of pregnancy The present investigation was begun on Aug 14, 1954, and the last patient was delivered in April, 1957

Method

Alternate patients, on their first examination at the clinics, were put into groups S and S— Group S were advised to take more salt in their diet—to use more salt in cooking, to add extra salt to their food at table, and to eat salt bacon, salt fish, and salted nuts, butter, &c Group S— were told to take less salt in their diet—to use as little salt as possible in cooking, to refrain from adding salt to their food at table, and to eat smoked bacon, unsalted butter, and unsalted fish, &c Otherwise the diets and other advice were the same in both groups At each visit their weight, blood-pressure, and urine tests were recorded, and they were reminded about their intake of salt according to their group Patients with a history of toxæmia were not excluded

Patients were considered to have toxæmia if their blood-pressure rose above 140/90 mm Hg with or without other symptoms They were also considered to have toxæmia if they had *œdema* and albuminuria without a rise in blood-pressure

At the first sign of toxæmia patients who had not booked a general practitioner were sent to hospital, where they were seen by an obstetrician who knew nothing of the patients' intake of salt He confirmed the diagnosis and admitted the patient to hospital for treatment On admission the intake of salt was stopped The liaison between the hospitals and the local-authority clinics is so close that it was possible for the investigator to follow the case-notes of each patient through to the end of the puerperium

All patients booked by general practitioners were sent home to bed The midwife in charge of the patient informed the general practitioner of what had been found and visited the patient at home about three times a week She kept a record of the patient's progress, and these

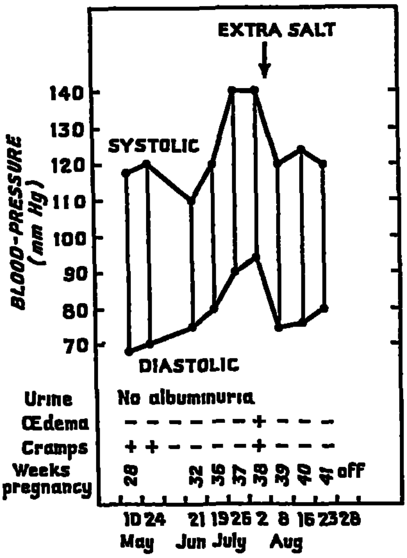

Fig 2—A mild case of toxæmia which cleared up completely

seen whether the symptoms disappeared or became worse

There were 28 women with toxæmia of pregnancy between the end of May and the end of September, 1957 8 of them had booked general practitioners and were not given extra salt but were referred, as usual, to their general practitioners, who either treated them at home or sent them to hospital These toxæmias followed the normal course and showed no sign of spontaneous recovery before delivery The other 20 patients had not booked a general practitioner and were advised to take extra salt This was their only treatment, they were not put to bed or told to rest, nor were they given sedatives

The 1st patient developed toxæmia at thirty-seven weeks' pregnancy She took more salt by adding as much salt as possible to her food Her symptoms had all disappeared in a week, and being better she spontaneously took less salt Next week her symptoms recurred She again took more salt and was again better in a week She then continued on her increased intake of salt until the end of her pregnancy and had no further symptoms of toxæmia (fig 1) This patient's weight again increased just before her blood-pressure rose, and returned to normal when she took more salt

The 2nd patient disliked salt and was put on six pills of sodium chloride a day Each pill contained gr 5, so she was taking gr 30 of sodium chloride daily Her blood-pressure never settled, it dropped to normal each afternoon and rose again every morning Her headache disappeared in twelve hours and never returned Her œdema went in four days and reappeared a few days later in her legs for a day Eight days after the onset of her toxæmia she was delivered of a normal full-time infant

A 3rd patient, who disliked salt, was put on twelve gr 5 pills of sodium chloride a day All her symptoms disappeared, but her blood-pressure never fell below 140/90 mm Hg, and on several days she had slight œdema of the legs only This patient and the 2nd patient were the only ones who had infarcted placentas

The remaining 16 patients were advised to measure out each morning four heaped teaspoonfuls of table salt and to see that by night they had taken all of it It was calculated that they took about gr 200–300 of sodium chloride daily The larger the amount taken the quicker was the recovery They found it easiest to take the bulk of this salt in orange-juice, lemonade, or lime-juice, the remainder being put on their food They were visited daily until all symptoms had disappeared All of them recovered completely and continued well on at least three heaped teaspoonfuls of table salt a day None of them had an infarcted placenta, and all gave birth to live full-term infants

In a 4th patient toxæmia developed about the thirtieth week of pregnancy She is 5-para with no history of previous toxæmia The blood-pressure rose first at the eighteenth week, and she was advised to take more salt At her next visit, her blood-pressure had dropped to normal, so she spontaneously cut off her extra salt This was not discovered until toxæmia developed at the twenty-ninth week She was then told to take three heaped large teaspoonfuls a day and recovered Her husband and two children developed influenza, and she was so busy nursing them and running the house that she had no time to measure out her daily salt As a result her blood-pressure again rose, but she had no recurrence of symptoms She was told that she could work as hard as she liked, provided she took four heaped teaspoonfuls of salt daily She again recovered, and was delivered, at forty-two weeks, of a living infant weighing 8 lb 6 oz , who cried lustily Macroscopically the placenta showed a few tiny patches of infarction round its edges

It was later found that large quantities of table salt often made the patients vomit Nausea and vomiting disappeared when they changed over to rock salt, but rock salt is more difficult to measure

It therefore appears that the 17 cases in group S were true toxæmias which recovered spontaneously because still more salt had been consumed after the symptoms had developed

Conclusion

Extra salt in the diet seems to be essential for the health of a pregnant woman, her fœtus, and the placenta

Summary

2077 pregnant women were investigated 1039 were told to take more salt and 1038 to take less salt

There was a lower incidence of toxæmia, œdema, perinatal death, antepartum hæmorrhage, and bleeding during pregnancy in those told to take more salt Other conditions were about the same in both groups Of those told to take extra salt 17 had transitory symptoms of toxæmia

20 women with early toxæmia were then treated with extra salt All of them improved, and the larger the dose of salt taken the quicker and more complete was the recovery The extra dose of salt had to be taken up to the time of delivery, otherwise the symptoms of toxæmia recurred Only early cases of toxæmia were available for treatment

My thanks are due to the Derby borough district midwives for their help in this investigation

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" Civil aviation enjoys a phenomenal safety record in comparison with that of the automobile, it being approximately forty times safer to fly on a scheduled airliner than to travel a like distance by auto But this wide variation would not exist if reasonable consideration had been given in earlier years to crash-safety design in automobiles If all automobiles were equipped with safety belts—and people wore them—adequate door locks to keep the occupants from cracking their skulls on the pavement, and delethalized interiors, the difference in the 'safety ratio' between airline and automobile travel would be reduced by at least one-half"—A HOWARD HASBROOK, *J Aviat Med* 1957, 28, 541

The mean weekly gain of weight was assessed in 844 patients who had attended the clinics regularly from less than twenty weeks' pregnancy to more than thirty-six weeks' pregnancy There were 422 cases in group S and 422 in group S— The mean weekly gain of weight was 0 95 lb in group S and 0 99 lb in group S—

In group S— some patients complained of severe backache, some of irritation of the skin of arms, legs, or abdomen, and some of weariness and stiffness in the limbs Others complained of falling because their legs suddenly gave way under them Sometimes this was so severe that they were afraid of going out of their houses or of crossing the road, in case they fell These symptoms did not develop in group S, and if they were present at the first examination they disappeared as soon as the women took more salt

TABLE VII—PREVIOUS TOXÆMIAS

Group	No	Recurrence	Raised B P	Alb	Raised B P Alb	Raised B P Œdema	Alb Œdema	Raised B P Alb Œdema
S	40	5	0	0	1	1	0	3
S—	39	13	2	1	1	5	0	4

Of all the cases diagnosed as toxæmia and sent to hospital only 2 were rejected as not being toxæmia The diagnosis of all the cases in group S— was confirmed by the hospital, and the patients were admitted for treatment The 2 cases rejected as not being toxæmia were in group S

The 1st case to be rejected was in a patient with a raised blood-pressure and no other symptoms of toxæmia She returned to the local-authority clinic and was encouraged to take still more salt, because it was thought that this would be sure to bring out her latent toxæmia A week later her blood-pressure had fallen to normal, and it remained down for the rest of her pregnancy No other symptoms of toxæmia developed, even though she kept up her increased intake of salt to the end

TABLE VIII—TOXÆMIAS AND OTHER ABNORMALITIES OF PREGNANCY

Group	No	Toxæmia	Perinatal deaths	A P H	Antenatal bleeding	Œdema	P P H	Premature births	Breech deliveries	Forceps deliveries	Cæsarean sections	Deformities
S	1019	38	27	17	27	163	47	86	23	22	9	25
S—	1000	97	50	32	50	287	50	89	29	19	14	22

After this case, all women, in both groups, with only a raised blood-pressure were watched for a week before being sent to hospital All such women in group S— had, by the end of the week, developed other signs of toxæmia and had to be sent to hospital, where the diagnosis was confirmed and they were admitted for treatment However, in group S, there were 4 women whose blood-pressure had dropped at the end of a week, no other signs of toxæmia developing They remained well throughout the remainder of their pregnancies

Meanwhile the 2nd case had been rejected by the hospital as not being a case of toxæmia

She had raised blood-pressure and albuminuria When seen at the local-authority clinic, she had been told to take still more salt in her food and to report at the hospital clinic almost a week later When she reported, her blood-pressure was normal and her urine clear She returned to the local-authority clinic and was advised to continue on her larger intake of salt She did so and remained well throughout the rest of her pregnancy

TABLE IX—STILLBIRTHS

Group	No	Grossly deformed	Apparently normal	Macerated	Fresh	Infarcted placentæ
S	20	7	13	4	9	4
S—	31	4	27	12	15	7

It was then realised that these transitory symptoms of toxæmia developed only in group S, and not at all in group S— It was thought that these symptoms might probably be due to the effect of the extra salt in the diet of these patients Since the symptoms were only transitory, it was decided that, in future, all women showing signs of toxæmia in group S would be told to take still more salt, and to report each week at the local-authority clinics In 11 cases the symptoms disappeared and never recurred throughout the remainder of the pregnancies Of these 11 patients 8 had raised blood-pressure and œdema, 2 had raised blood-pressure, albuminuria, and œdema, and 1 had albuminuria and œdema

TABLE X—NEONATAL DEATHS

Group	No	Deformities	Cerebral hæmorrhage	Respiratory syndrome	Fibrocystic disease
S	8	3	1	4	0
S—	21	4	2	14	1

When the investigation had ended and the data had been collected, the question arose what were these cases with transitory symptoms of toxæmia? Were they toxæmias which had spontaneously recovered, or were they not toxæmias at all? No similar cases had occurred in group S— Since it had been ultimately found that the incidence of toxæmia was much lower in group S than in group S—, it was difficult to believe that the extra salt in the diet had been the cause It was decided that, in future, women with toxæmia of pregnancy should be treated with extra salt in their diet Then it would be

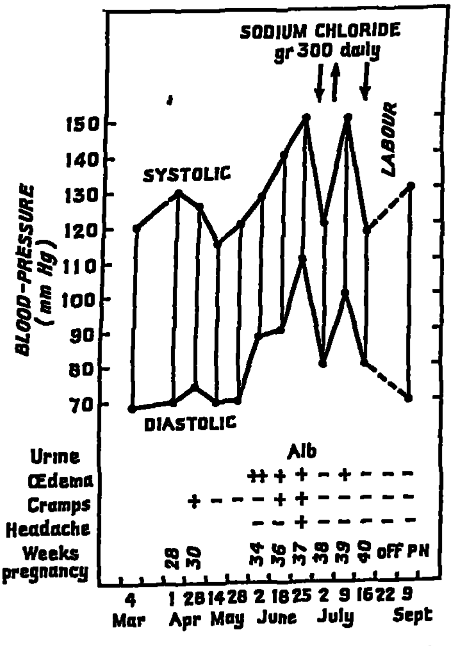

Fig 1—When salt was reduced (as indicated by the upward-pointing arrow) symptoms recurred They disappeared when salt was again increased (P N = postnatal)

walking, however, was still unsteady, she staggered and fell easily but did not stagger or fall in any particular direction She seemed to walk on rather a wide base. At the time of discharge there was no real evidence of any ataxia. Her coordination in general was slower and less harmonious than normal for her age but could be accepted as not incompatible with the degree of her mental impairment. Owing to the degree of mental impairment it had been impossible to apply adequately any finer test to ascertain or define the individual component factors in her incoordination

Previous history—The patient had been born at full term by normal delivery at home. There were no complications at birth The neonatal period was uneventful She was artificially fed and in the first few months had a moderate amount of vomiting, which led to a trial of many different brands of dried milk. She was eventually given sterilised cow's milk and from then on had no more vomiting In spite of the vomiting she had steadily gained weight. Her mother described her as a "lovely bonny happy baby" and did not consider that there had been any delay in smiling, sitting up, or walking (sat up at 8 months and walked at 11 months), but she felt quite early that the patient was backward like her brother (case 2), but only in speech. She had measles and chickenpox at the age of 1 year (case 2 and other sibs had the same illnesses at this time) Each illness was mild, and there were no unusual symptoms or complications She had a period of about a week's duration of convulsions in January, 1955 The convulsions were very slight ("just in and out" in her mother's words) They were symmetrical and generalised and occurred once or twice a day Her doctor (Dr J Edwards) prescribed sedation. Hospital advice was not sought. There was no known precipitating factor, and the child was apparently apyrexial throughout. For about 2 weeks after this the mother noticed that the patient was unsteady in her hand movements She did not think that there was any unsteadiness in walking or that the patient walked less well than before this 14-day period Thereafter until the time of her admission to hospital (Oct 29, 1955) her mother had not considered that there was any abnormality of coordination but after her discharge on Dec 8, 1955, her mother noticed that the patient walked unsteadily and fell easily She said that the child walked "sort of sideways", and that sometimes, even when standing, "her legs would just give way and down she would go" She did not notice any incoordination of the patient's upper limbs

Investigation and reports—The blood findings are given in table I The urine appeared normal on routine examination, no phenylpyruvic acid was found Mantoux negative. White-cell count normal with normal differential Blood-film normal, no punctate basophilia Throat swab no pathogens Lumbar puncture on Nov 3 and 22, 1955, clear fluid, pressure normal, cells less than 1 per c.mm, protein 20 mg per 100 ml Radiography of long bones, skull, and chest normal Urinary lead not abnormal Finally, on chromatography an unusual urinary aminoacid was found by one of us (V K. W) and was further studied at University College Hospital

TABLE I—BIOCHEMICAL FINDINGS IN SERUM (OR PLASMA) OF AFFECTED SIBS

—	Case 1			Case 2	
	Admission no				
	1	2	3	1	2
W R. and Kahn	Neg	Neg		Neg	
Urea (mg per 100 ml.)	30·0	27·0	21·0	32·0	24·0
Calcium (mg per 100 ml.)	11·[illegible]	10·7	10·4	10·6	9·5
Sodium (mEq per Litre)		137·0	144·0	139·0	1[illegible]8·0
Potassium (mEq per Litre)		5·1	4·1	4·1	4·1
Cholesterol (mg per 100 ml)		210·0	160·0	190·0	170·0
Phosphate (mg per 100 ml.)		5·8	4·8	5·7	4·5
Chloride (mEq per Litre)		100·0	103·0	101·0	105·0
Bicarbonate (mEq per Litre)		21·0	15·2	21·8	24·9
Total protein (g per 100 ml.)		6·0		6·2	
Albumin (g per 100 ml)		3·7		3·9	
Globulin (g per 100 ml)		2·3		2·3	
Electrophoresis (paper strip)		Normal		Normal	
Alkaline phosphatase (K-A units)		2[illegible]·0	23·5	23·0	24·5
Magnesium (mg per 100 ml)		2·8		2·3	
Fasting blood-sugar (mg per 100 ml)		75·0		75·0	

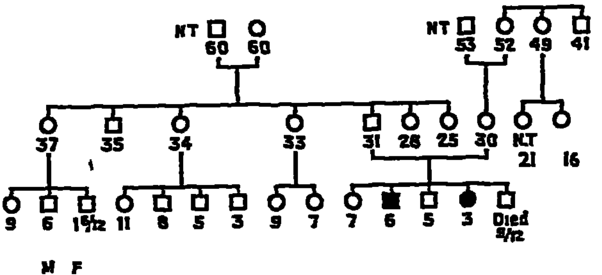

Fig 1—Family tree.

Patient's family—In view of the possibility that an inborn error of metabolism was responsible for the patient's disorder, her whole family were investigated, especially as regards their urinary output of aminoacids This was done thoroughly with the help of Dr H Harris The pedigree is shown in fig 1 The near relations were then interviewed. The father was a healthy lorry driver of average intelligence, the mother was a healthy woman of intelligence above average. Their children consisted of (1) V, a healthy intelligent girl aged 7 years, (2) K (case 2), a boy aged 6 years, who was healthy but attended a school for backward children, (3) C, a healthy intelligent boy aged 5 years, (4) M, and (5) D, a boy who died of bronchopneumonia at the age of $4^1/_2$ months The parents were not consanguineous There was no history of abortions or miscarriages The first four sibs were born at home and appeared normal at birth. The fifth child was given an exchange transfusion at the age of 4 hours for Rh (D) incompatibility After this he had cerebral manifestations in the presence of fairly deep jaundice but made an apparently satisfactory recovery A female cousin, aged 11 years, had had fits in infancy, but we have not seen or examined this child Otherwise there was no ascertainable history of mental defect, neurological disease, fits, or other possibly relevant factor in the family In view, however, of the mental defect in the second sib, K., and since his urinary aminoacid chromatogram showed a gross aminoaciduria abnormality identical with that already found in M, arrangements were made to admit both affected sibs to West Park Hospital, Macclesfield, for further study

Readmission—M. was admitted on Feb 15, 1956 Since Dec. 8, 1955, she had remained well The phenobarbitone had been discontinued a month before readmission, but there had been no further convulsions There was no ataxia Biochemical findings are shown in table I Intravenous pyelography showed that both kidneys excreted the dye normally No lesion of the urinary tract was found Blood picture normal Red-cell fragility normal Coombs test negative Urine normal on routine examination van den Bergh no direct reaction. Bilirubin less than 0·5 mg per 100 ml Thymol turbidity 3 units Thymol flocculation – Cerebrospinal fluid (C.S.F) clear, colourless, and containing no cells, sugar 75 mg per 100 ml, chlorides 770 mg per 100 ml, and protein 10 mg per 100 ml. Pandy negative Lange gold showed no change.

Electrocardiography—On Nov 29, 1956, Dr A Hollman reported "Semi-vertical heart with ST depression in V4, aVL, and I, and T-wave inversion in V7, aVF, and III R/S rate of 0·30 in lead V1 is rather low but is borderline normal for age The changes are consistent with left ventricular hypertrophy"

Electroencephalography—The resting record showed spasmodic bursts of medium-voltage alpha rhythm at 8 c/s in the occipital and preoccipital areas, bilaterally synchronous and symmetrical The dominant rhythm was of medium-voltage theta activity at 4–6 c/s seen in all areas, symmetrical, and bilaterally synchronous There were occasional diffuse bursts of high-voltage delta activity at $3^1/_2$–4 c/s, which were symmetrical and predominantly out of phase on the right Low-voltage beta

A DISEASE, PROBABLY HEREDITARY, CHARACTERISED BY SEVERE MENTAL DEFICIENCY AND A CONSTANT GROSS ABNORMALITY OF AMINOACID METABOLISM

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There is no need to stress the problems posed by the large numbers of mentally defective people, and by our few present hopes of fully corrective therapy A milestone in the modern development of our knowledge occurred with the discovery of the specific hereditary form of mental deficiency called phenylketonuria (Folling 1934), especially because of its association with a comparatively simple disorder of phenylalanine metabolism—simple, that is, when compared with the complexity of the biochemistry in other hereditary forms of mental deficiency such as Tay-Sachs disease, or gargoylism Since that time further discoveries have been made of more simple biochemical disorders in various forms of mental deficiency and in closely related neurological or medical conditions for instance, galactosæmia (reviewed by Holzel et al 1957), Wilson's disease (reviewed by Bearn 1957), the so-called "organic aciduria" syndrome (Lowe et al 1952, Dent and Harris 1956), and recently of H-disease (Baron et al 1956), and of goitrous cretinism (reviewed by Stanbury and McGirr 1957)

In each of these instances compounds of well-known chemical structure are involved Since something is already known about their metabolism, one can immediately speculate about possible forms of therapy and, in some cases—e g, phenylketonuria and Wilson's disease—begin seemingly rational therapeutic trials A further point of interest is the fact that the biochemical disorder, when known, may be so gross, easy to detect, and constantly present as to remove any difficulty in diagnosis

It also seems to be of especial significance that all the disorders mentioned above are hereditary Clearly there are likely to be many more such diseases which have so far escaped recognition, but with the development of paper chromatography, by which body fluids can easily be scanned for the presence of abnormal quantities of hundreds of known or likely metabolites, we can reasonably expect many important discoveries to be made in the near future

We describe here preliminary studies of a further disease of this type These studies began in October, 1955, when a girl apparently suffering from idiopathic epilepsy was admitted under one of us (J D A) Her subsequent progress did not conform to the usual pattern of such epilepsy After the cessation of the convulsive period, and in the absence of further convulsive episodes, she exhibited general ataxia This unusual feature, with the fact that the child was severely mentally retarded, and our subsequent failure to establish an organic neurological cause or systemic disease, suggested a metabolic disorder such as hypercalcæmia or lead poisoning Chromatography (V K W) then revealed the presence of a gross abnormality of urinary aminoacids Study of the girl's relations later revealed that an identical abnormality was present in a male sib who also has a severe mental defect

Case-reports

Case 1 —A girl, M, aged 3 years 5 months, was admitted to Stepping Hill Hospital, Stockport, as an emergency on the evening of Oct 29, 1955 She was conscious but not cooperative and was considered to be recovering from convulsions She had been quite well up to mid-morning of that day, but between then and admission she had had five convulsive seizures of increasing severity and duration, the last shortly before admission In each she had been unconscious, but in none had she been incontinent From the description it appeared that there had been symmetrical generalised clonic movements of face, arms, and legs The first attack had lasted 2 or 3 minutes, and the last 15–20 minutes There was nothing to suggest a precipitating cause, she was apyrexial, and there was no history of injury

General examination, apart from a moderately loud (grade-3) musical systolic murmur, maximal along the left sternal border, was negative Examination of the nervous system revealed no abnormality except that the Babinski reflex on each side was equivocal

Treatment and progress —She was placed on routine sedation (phenobarbitone), the provisional diagnosis being idiopathic epilepsy During the night she had one further convulsion, of a generalised epileptiform type, lasting a few minutes In the morning she seemed brighter She continued apyrexial but had developed purulent rhinorrhœa, and her fauces were thought to be injected Prophylactic parenteral penicillin was given and continued for the next five days The plantar response after admission became flexor bilaterally Four days after admission (Nov 2, 1955) at short intervals *(1 hour)* during the morning there were three further similar convulsions The patient was then still apyrexial There were no more convulsions thereafter during her stay in hospital (discharged Dec 9, 1955) During this time she was maintained on phenobarbitone, and she was discharged on prophylactic doses On Nov 16, 1955, she had pyrexia *(100 5° F)* for the first time, it lasted 5 days, the highest recorded temperature being 102 4°F and was considered to be due to an *Escherichia coli* pyelitis and was treated with sulphadiazine

Mental condition —Though, for a day or two after admission, we had been inclined to attribute her failure to speak and cooperate in general to a combination of her new environment and the effect of the epileptiform seizures, we realised at this time that she had a severe degree of mental retardation On the sixth day after admission (Nov 4, 1955) she had severe ataxia (she had had three convulsions on Nov 2, 1955) Ataxia was first seen in her arms, being particularly noticeable during attempts to pick up a cup and feed herself The degree of incoordination was such that she could not complete these simple movements and had to be fed, but she had no difficulty in swallowing and no choking There was no apparent anomaly of any cranial nerve, in particular no nystagmus The incoordination resembled that of a severe chorea, with a suggestion of an athetoid overlay, and occurred only on voluntary action Both arms were equally affected We could not examine the coordination of her legs other than to establish that she could not stand or walk Tone was normal From this day on, there was a steady, quite rapid, and general diminution in the degree of incoordination By Nov 15, 1955, she could coordinate fairly well she could feed herself and walk Her

TABLE II—BLOOD-GROUPS

Father	Mother	Case 2	Case 1	Brother	Sister
O	O	O	O	O	O
R_1r	rr	R_1r	R_1r	rr	rr
MNs	MNs	MNs	MNs	MNs	MNs
P−ve	P−ve	P−ve	P−ve	P−ve	P−ve
Le(a+b−)	Le(a−b−)	Le(a−b−)	Le(a−b−)	Le(a−b−)	Le(a+b−)
Lu(a−)	Lu(a−)	Lu(a−)	Lu(a−)	Lu(a−)	Lu(a−)
kk	K+ve	K+ve	K+ve	kk	kk
Fy(a+)	Fy(a+)	Fy(a+)	Fy(a+)	Fy(a+)	Fy(a+)
Jk(a+)	Jk(a+)	Jk(a+)	Jk(a+)	Jk(a+)	Jk(a+)

Our final opinion of coordination in these two children was that in each there was some slowness and slight clumsiness in the general execution of movement, the degree of which, however, we did not consider to be incompatible with the respective degree of mental impairment

Intellect

The severity of the intellectual impairment in each case was confirmed by the I Q rating (Dr R Cargill) case 1's Gesell rating was 32, and case 2's intelligence quotient on the Terman-Merrill scale was 50 Case 1 had a vocabulary of about 12 words, but case 2 had about 50 words Case 1's perception seemed to be of a higher standard than her execution Each child was docile, and there did not appear to be any emotional disturbance in either

Cardiovascular System

The murmur heard in each child was similar in location, character, and intensity Clinical examination of the heart in each case revealed no other abnormality, and this was confirmed radiologically It is thought possible that each child has an interventricular septal defect

a *b*

Fig 3—Standard urine aminoacid chromatograms *a* case 1, *b*, case 2.

Note extraordinary similarity between these two affected sibs and great difference from published normals (Dent and Walshe 1954) In each chromatogram the strongest spot is the unknown aminoacid and the weak spot above and slightly to the left of it is the substance to which it can be readily converted by hydrolysis

Blood-groups

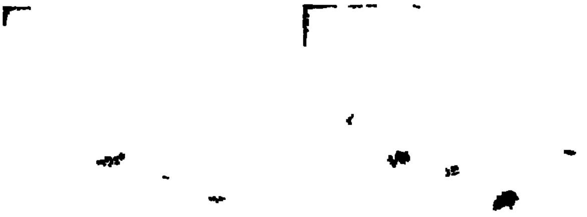
We are indebted to Dr F Stratton for determining the blood-groups (table II) It is presumably a chance finding that the two sibs have identical phenotypes

Alkaline Phosphatase

In each child the level of alkaline phosphatase, on each occasion on which it was estimated, was moderately high We cannot offer any explanation of this Though it was established in the mother's third and fourth pregnancies (fig 1) that there were then no maternal antibodies which might produce fœtal kernicterus, the ataxia seen in case 1 and the type of ambulation in case 2 in infancy might in each instance have been caused by abnormality of the basal nuclei Liver function, assessed by our empirical tests, was not disturbed, but, since a high alkaline-phosphatase level may be a sign of liver disease, further attention should perhaps be given to this abnormality

Urinary Excretion of Aminoacids

Since the discovery, in the urine of both case 1 and case 2, of a grossly abnormal aminoacid excretion, which was not present in the urine of other members of their family, repeated analyses of further samples of their urine have confirmed the original findings The abnormality appears to be constant qualitatively and quantitatively in both children The nature of this may be seen from fig 3 It will be noted that it mainly comprises the excretion of a large amount of one ninhydrin-reacting substance,* but there is a small amount of another substance close to it on the chromatogram Neither of these can be matched in their chromatographic behaviour with any of the known aminoacids in our very large collection of these compounds, or with any of our catalogued "unknowns" such as have been found, for instance, as a result of detailed studies of normal urinary constituents by Westall (1955) It is also remarkable that the aminoacids normally excreted—e g, glycine, alanine and taurine—are, if anything, excreted in this urine in smaller quantities than usual

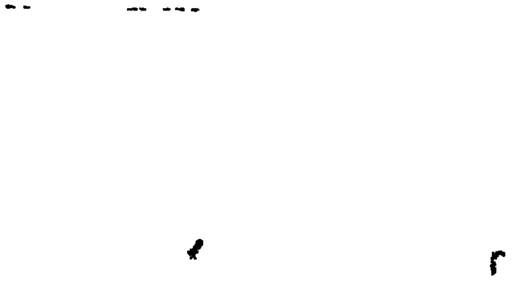


a *b*

Fig 4—Standard aminoacid chromatographs of plasma: *a*, case 1, *b*, case 2

The weak spot low down on the right in both cases is the unknown aminoacid Immediately above it is a strong spot due to glutamic acid This spot is unusually strong owing to its formation from glutamine during storage of the specimen The other aminoacids present are otherwise quite normal

We cannot yet suggest any chemical structure for the main urinary constituent It has not so far reacted with reagents which we have tried for specific chemical groupings—e g, indole, glyoxaline, and ester phosphate—or with tests likely to reveal dicovalent sulphur The main spot is very easily hydrolysed to the subsidiary spot (also unidentified) which appears weakly immediately above and to the left of it on the urine and C S F chromatograms (figs 3 and 5) The change goes virtually to completion in 5 *N* hydrochloric acid at 100°C



a *b*

Fig 5—Standard aminoacid chromatograms from C.S F *a*, case 1, *b* case 2.

These are quite normal except for the large strong spot low down to the right which is due to the unknown aminoacid Note how much stronger this substance is here than in the plasma Equal volumes of C S F and plasma were analysed on these chromatograms activity at 18–22 c/s underlay the record and was superimposed upon the slower components The record was abnormal It showed cerebral dysrhythmia, which was predominantly in the right hemisphere No typical epileptic features were seen

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* Further work on the identification of the unknown ninhydrin-reacting substance in the urine of the two affected sibs suggests strongly that it is not (as we have assumed above) a single aminoacid but a peptide which is rather resistant to acid hydrolysis

Discharge —The patient left hospital on Aug 10, 1956

Readmission —The patient was readmitted for a week from Jan 17 to 24, 1957, to University College Hospital Since her previous admission she had had no further fits and in her general health had remained well No further signs of disease were noted The cardiac murmur was still present The blood-pressure was 95/70 mm Hg The biochemical findings are given in table I Routine urine and renal-function tests gave normal results Skeletal radiographs were normal

Case 2 —M 's elder brother K , aged 6 years 3 months, was admitted on Feb 15, to West Park Hospital and discharged on Aug 10, 1956 He had been born at full term by normal delivery at home There were no complications at birth The neonatal period was uneventful He was fed on dried milk and throve well but was never an eager feeder He smiled at 5 months, sat up at 7 months, and walked at 13 months His mother did not consider that he was backward in anything except speech This delay in speaking she attributed to deafness, but she had him examined at the age of $2^1/_2$ years at Manchester Royal Infirmary by Professor Ewing, who excluded any auditory abnormality From then she had accepted the patient as backward He had never had any fits, and his only previous illnesses had been measles and chickenpox at the age of 4 years at the same time as case 1 and their sibs These illnesses were mild and uncomplicated He had sustained one accident at the age of 4 years 9 months he was knocked down by a car, was not unconscious, and sustained only minor injuries He was treated at home His mother said that he had never had any unsteadiness like M but " seemed to keep his legs a bit bent at the knees and to take quicker and quicker steps as he went forward, often ending in falling forward "

Examination —General examination was negative except that, like M , he had a moderate (grade-3) musical systolic murmur maximal along the left sternal border The continuing severe mental retardation was noted It was also observed, as in case 1, that the hair was abnormal (see below)

Investigations —Biochemical findings are given in table I Skeletal radiography, screen of heart, and intravenous pyelography normal Full blood-count normal Red-cell fragility and Coombs test normal Routine examination of urine normal van den Bergh no direct reaction Serum-bilirubin less than 0 5 mg per 100 ml Thymol turbidity 2 units Thymol flocculation negative C S F clear and colourless, containing no cells, sugar 75 mg per 100 ml , chloride 750 mg per 100 ml , and protein 10 mg per 100 ml Pandy negative Lange gold test normal

Electrocardiography —On Nov 29, 1956, Dr Hollman reported " There is a dominant R in V1 with an R/S ratio of between 1 7 and 2 5, which is definitely abnormal at this age and consistent with right ventricular hypertrophy There is also slight ST depression in aVL, which may indicate left ventricular involvement The QTC is prolonged at 0 440 "

Electroencephalography —The resting record shows spasmodic bursts of high-voltage alpha rhythm at 8 c/s in the occipital areas There were occasional bursts of low-voltage or medium-voltage beta activity at 18–20 c/s in all areas High voltage theta activity was the dominant rhythm at 4–6 c/s in all areas Associated with this were occasional high-voltage spikes, which are out of phase throughout the right hemisphere There were numerous bursts of diffuse high-voltage spike and wave activity at 3–$3^1/_2$ c/s They were symmetrical and consistently out of phase on the right The record was abnormal There was definite evidence of epilepsy dominating the right hemisphere, with occasional spread to the left

Readmission —The patient was readmitted for a week from Jan 17 to Jan 24, 1957, to University College Hospital Since his previous admission he had had no fits and had been in good general health No further signs of disease were noted The cardiac murmur was still present The blood-pressure was 110/70 mm Hg His hair had grown a little better and required occasional cutting The biochemical findings are given in table I Routine urine and renal-function tests gave normal results Skeletal radiographs were normal

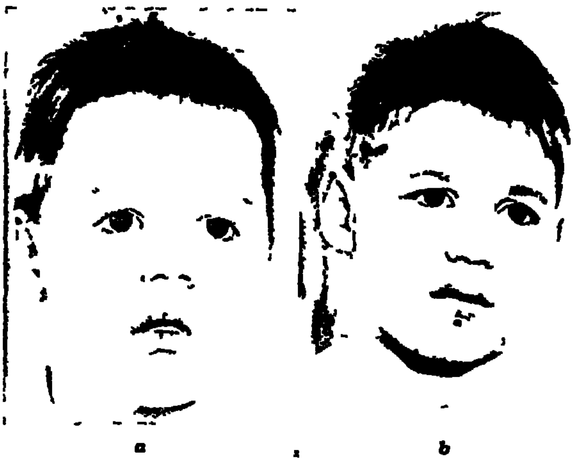

Fig 2—The affected sibs *a*, case 1 (M); *b*, case 2 (K)

Further Observations on the Two Affected Sibs

Facial Appearance

The affected sibs bore a striking resemblance to each other (fig 2) Their expression also was the same, being sad and wistful

Hair

Their hair was light brown, dry, and friable Its growth seemed to be irregular, giving a tufted, almost matted, appearance It was difficult to comb or brush into any semblance of tidiness The ends were frayed and they seemed to break off abnormally easily, particularly over the occipital region, presumably owing to its being the area of greatest friction

Their mother had noticed that their hair was not *like that* of the other two living sibs She described it as " different—goes very brittle—comes out on the comb and leaves a stubble " She thought the " coming out " was particularly noticeable in November and December She stated, however, that K had " beautiful curly " hair until the age of 15 months, and that case 1's hair also was normal in infancy The hair of the father, mother, and the other two living sibs *was normal* (for colour of hair see below)

Skin

M 's skin was slightly rough on the arms and on the dorsum of the hands but elsewhere normal The texture of case 2's skin was normal In both children perspiration appeared to be normal Except that case 2 had an area of pigmentation near the lower half of his right sternomastoid muscle and as large as a silver threepenny piece, there were no other lesions (xanthomatous, vascular, pigmentary, or other) in either child The teeth and nails were normal Lacrimation and salivation were normal Case 1's eyes were grey and case 2's light brown

Electroencephalography and Neurology

In both children the electroencephalograms were grossly abnormal (see above) Case 2, whose electroencephalograms showed definite evidence of epilepsy, had no clinical manifestations, whereas case 1, in whose electroencephalograms " no typical epileptic features were seen ", had epileptiform seizures We are indebted to Dr C E Smyth for the electroencephalograms and for his further neurological opinion as follows " So far as I am concerned, I could find no evidence of gross cerebral disease in either of them They are, of course, backward There is no evidence of any motor disturbance, and I thought their fundi were normal There were no superficial anomalies of the skin and no enlargement of liver and spleen I cannot really throw further light on this problem " disease cannot be normally dealt with If this is so, its normal concentration in the body must be exceedingly low because it does not seem to have been found before by other workers studying brain extracts or biological fluids, and was not even found by Westall (1955) in his very detailed study of the aminoacid composition of normal urine, a study based on an analysis by micro methods of concentrates from 100 litres of normal urine

It is intriguing to consider the strong possibility that an organic cardiac lesion also exists and is related to the biochemical abnormality With the discovery of serotonin (5-hydroxytryptamine) and of the cardiac lesions associated with its overproduction by argentaffinomata (Sjoerdsma et al 1956) the stage is set for the association of further cardiac lesions with other humoral factors

Our further consideration of the cause of the disease and of its possible treatment must await identification of the unknown substance The disease is certainly extremely rare because, apart from the fact that we and others have never observed it in the course of many thousand chromatographic examinations of urine, a deliberate search for the condition among 1500 mentally defective patients has so far failed to reveal a further case (H Harris, private communication) This search is being continued

Summary

A family is described in which two of four children of unrelated parents show a severe degree of mental retardation

Both affected sibs have grossly abnormal electroencephalograms One has had several epileptiform convulsions followed by ataxia of a few days' duration Both sibs have friable hair and systolic murmurs but are otherwise healthy and normal on physical examination

The two affected sibs have an identical and highly specific gross disorder of aminoacid metabolism not present in any other members of the family This is most easily shown by the constant excretion in their urine of large quantities of a new and still unidentified substance There are also minor changes in the pattern of the aminoacids excreted

The abnormal substance was found in low concentrations in the plasma of the affected children but was present in very much higher concentration in their C S F It seems possible that it is formed in the brain or in some other organ in close association with the C S F, whence it leaks out into the plasma and is rapidly excreted by the kidneys

Apart from acknowledgments already made in the text, we wish to thank also Miss V Ward for technical assistance and Miss B Warland for help with the family survey

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CHRONIC ASTHMA TREATED WITH POWDER INHALATIONS OF HYDROCORTISONE AND PREDNISOLONE

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MANCHESTER ROYAL INFIRMARY

OUR small trial of the treatment of chronic asthma with aerosol hydrocortisone proved disappointing (Brockbank et al 1956) Better results have been obtained in a blind trial of hydrocortisone and prednisolone powder inhalations The manufacturers kindly provided us with hydrocortisone ('Cortef'), a much smaller supply of prednisolone ('Delta Cortef'), and an undetectable blank inert powder consisting of lactose and 1% calcium stearate, all in sausage-shaped capsules, for use in a special inhaler

Method

The materials were placed in numbered bottles in random order by a member of the staff of the Department of Medicine and were used in number sequence on patients whom we considered to be suitable for trial These all had chronic asthma and used much antispasmodic material They were seen by us at least a week before they were included in the trial and were not improving spontaneously during this period When the trial was completed, we assessed each case and reported to our colleague and learnt for the first time what had been in each bottle

Each patient was provided with fourteen capsules, which needed pricking with a pin at one end before use The capsule was then inserted in the inhaler, pinhole uppermost Sharp pressure on the rubber bulb jerked the capsule upwards until its progress was checked, thus expelling a surprising amount of powder

The patient was instructed to use the inhaler thrice daily irrespective of spasm On each occasion the bulb was to be given three good sharp squeezes, holding the inhaler upright in the mouth and breathing in at the critical moment Care had to be taken not to breathe out into the inhaler, otherwise the moisture caused the powder to clog

When the capsule was half empty it was taken out, and the top half was removed The inhaler and capsule had then to be kept upright, or the powder spilled out One capsule lasted on average five days The period of treatment was about seventy days and was followed by a month without any of the powder inhalation

Patients were instructed to use their own antispasmodic material as required, but in successful ("much improved") cases the need for this vanished They were also asked to keep a diary of the number of attacks of spasm and the amount and type of antispasmodic material required during the trial

Each hydrocortisone capsule contained 15 mg of the acetate (equivalent to 13 4 mg of hydrocortisone base), making the daily dose 3 mg Each prednisolone capsule contained 5 mg, making the daily dose 1 mg

TABLE I—ANALYSIS OF MATERIAL

Treatment	No and sex of patients	Age (yr)	Duration of asthma (yr)
Hydrocortisone	24 (8M 16F)	16–63 (av 42)	0 5–45 (av 13)
Prednisolone	7 (3M 4F)	26–57 (av 44)	3–30 (av 13)
Blank	13 (6M 7F)	25–66 (av 45 5)	3–32 (av 14)
Total	44 (17M 27F)	16–66 (av 43)	0 5–45 (av 13)

in 15 minutes. If the urine is not fresh, at least two further unidentified ninhydrin-reacting spots are seen on the chromatogram in addition to the main spot, these also being presumably decomposition products of the main spot. The production of one of these further spots also appears to occur on electrolytic desalting of the urine. A large stock of these compounds in the crude state has been isolated from the urine for identification.

Chromatograms of the plasma and C.S.F. were also prepared according to our standard methods (Dent 1951) and are shown in fig. 4. The low plasma concentration of the unknown spot occurring in the presence of a very high urinary output suggested a high renal clearance and was confirmed for case 2 by determining his renal aminoacid clearances in a fasting 3-hr. urine collection and collections of blood at 1 and 2 hr. pooled before being analysed by the Moore and Stein (1954) method. The clearance of the unknown spot was 105 ml. per min. per 1.73 m.^{2}, suggesting that little or none of the compound is reabsorbed by the renal tubules. If its molecular weight is 150 and it reacts with ninhydrin to give the same colour as does leucine, the plasma level of the unknown compound was 1.7 mg. per 100 ml. and the average urine output over the 3-hr. period was 1.8 mg. per min. per 1.73 m.^{2}, corresponding to a 24-hr. fasting excretion of about 2.5 g. per 1.73 m.^{2} or an actual uncorrected output of 1.3 g. in case 2. The high C.S.F. level seen on the paper chromatograms was fully confirmed on Moore and Stein analysis, which gave values of 4.2 and 5.1 mg. per 100 ml. for cases 1 and 2 on the same assumptions as stated above, this being 2.5–2.9 times higher than the plasma level. No other aminoacid concentrations, excretions, or clearances were disordered to any comparable extent.

Head Size

Prof. L. S. Penrose reported as follows:

Case 1, aged 4 years: length 131 mm., breadth 168 mm. Norms for female aged 4 years are 134 mm. and 169 mm. respectively.

Case 2, aged 7 years: length 135 mm., breadth 175 mm. Norms for male aged 7 years are 141 mm. and 179 mm. respectively.

Both children have normally shaped heads but with dimensions below the average. In neither case is the deviation sufficient to be classed as abnormal, but in case 2 it is borderline.

Hair Colour

Specimens of hair from parents and four children were examined, and the reflection of light over the range of the visible spectrum was measured by Dr. N. A. Barnicot, who reported as follows:

"As is usual, the four children have hair of lighter shade than that of their parents because of the normal tendency for hair to darken with advancing age. There is no apparent tendency for the affected children's hair to be lighter in colour than that of their normal sibs. One specimen of case 1's hair, taken on Dec. 5, 1956, seems to be of rather brittle texture, but it is difficult to demonstrate this unequivocally, and specimens taken since then seem normal."

Discussion

The clinical aspects of this form of mental deficiency have nothing particularly characteristic about them. This will make clinical detection of further cases rather difficult, especially in the first year of life, during which they had appeared to develop normally. The unusual behaviour of M. after her epileptic seizures is perhaps not so surprising in view of her very severe mental deficiency. Presumably disturbances produced by epilepsy are much more severe when cerebral function is already grossly subnormal. The excessive friability of the hair was certainly unusual. The friability was somewhat variable, for M., when first seen, had a short crop of hair which did not need cutting and did not for some time grow longer. A year later it had grown better and was a few inches longer in places. There were no other ectodermal abnormalities that we could discover.

The fact that the two sibs were so similarly affected is of great importance, and it will be necessary in future to confirm that this means, as we think very likely at the moment, that the disease is hereditary. We could not discover any possible environmental factors that might have been operative, and rhesus incompatibility was adequately excluded. The fifth sib required an exchange blood-transfusion at birth because of hæmolytic disease. However, no antibodies were found when the mother had been examined during the third and fourth pregnancies and they did not appear till the end of the fifth pregnancy.

The discovered biochemical abnormality was quite spectacular. The unknown substance was found in all specimens of urine of cases 1 and 2 that were examined; all the other members of the family had normal aminoacid patterns shown by paper chromatography. These all-or-none findings argue in favour of a genetic causation. The unknown substance was excreted in very large quantity, and the other aminoacids normally excreted in urine were present, if anything, in smaller quantities than usual (fig. 3).

Our analyses of the C.S.F. and of the plasma of cases 1 and 2 are especially interesting. In healthy people the aminoacids that are present in the plasma are all present in the C.S.F. in greatly reduced concentrations, except glutamine, which is present in about the same concentration. In phenylketonuria, in which the biochemical abnormality—namely, inability to metabolise phenylalanine—is present in the liver, phenylalanine accumulates in the plasma and is thereupon excreted into the urine by an overflow mechanism, and it leaks also into the C.S.F. to reach a concentration of about a third of that in the plasma. In the disease we have here described the situation is entirely different. As can be seen from the paper chromatograms, and confirmed by quantitative analysis, the C.S.F. concentration of the unidentified aminoacid (fig. 5) is much higher than in the plasma (fig. 4), about 2.5–2.9 times or so as high. This suggests at once that the substance is formed not by a defective enzyme in the liver or in any other organ in close relationship to the systemic blood-supply but in the brain or in some other structure closely associated with the C.S.F. It leaks, presumably, from there into the blood-stream, whence it is rapidly excreted by the kidney into the urine, probably without any tubular reabsorption. This latter situation seems to occur when other presumed purely intracellular substances find their way into the plasma, which they do not normally use as a means of transport. Examples of such compounds are phosphoethanolamine (our unpublished results on the study of hypophosphatasia), homogentisic acid (Neuberger et al. 1947), β-aminoisobutyric acid, at least in high excretors of this substance (Evered 1956), and porphobilinogen (Goldberg and Rimington 1954). The mechanism of excretion in such cases is not fully described in terms of the definitions previously made of "renal" and "overflow" mechanisms (Dent and Walshe 1954). Perhaps it should be called a "no-threshold" aminoaciduria.

Our present speculation is therefore that the disease has revealed for us a substance which is normally produced by and metabolised in the brain but which in this disease cannot be normally dealt with. If this is so, its normal concentration in the body must be exceedingly low because it does not seem to have been found before by other workers studying brain extracts or biological fluids, and was not even found by Westall (1955) in his very detailed study of the aminoacid composition of normal urine, a study based on an analysis by micro methods of concentrates from 100 litres of normal urine.

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CHRONIC ASTHMA TREATED WITH POWDER INHALATIONS OF HYDROCORTISONE AND PREDNISOLONE

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MANCHESTER ROYAL INFIRMARY

OUR small trial of the treatment of chronic asthma with aerosol hydrocortisone proved disappointing (Brockbank et al. 1956). Better results have been obtained in a blind trial of hydrocortisone and prednisolone powder inhalations. The manufacturers kindly provided us with hydrocortisone ('Cortef'), a much smaller supply of prednisolone ('Delta Cortef'), and an undetectable blank inert powder consisting of lactose and 1% calcium stearate, all in sausage-shaped capsules, for use in a special inhaler.

Method

The materials were placed in numbered bottles in random order by a member of the staff of the Department of Medicine and were used in number sequence on patients whom we considered to be suitable for trial. These all had chronic asthma and used much antispasmodic material. They were seen by us at least a week before they were included in the trial and were not improving spontaneously during this period. When the trial was completed, we assessed each case and reported to our colleague and learnt for the first time what had been in each bottle.

Each patient was provided with fourteen capsules, which needed pricking with a pin at one end before use. The capsule was then inserted in the inhaler, pinhole uppermost. Sharp pressure on the rubber bulb jerked the capsule upwards until its progress was checked, thus expelling a surprising amount of powder.

The patient was instructed to use the inhaler thrice daily irrespective of spasm. On each occasion the bulb was to be given three good sharp squeezes, holding the inhaler upright in the mouth and breathing in at the critical moment. Care had to be taken not to breathe out into the inhaler, otherwise the moisture caused the powder to clog.

When the capsule was half empty it was taken out, and the top half was removed. The inhaler and capsule had then to be kept upright, or the powder spilled out. One capsule lasted on average five days. The period of treatment was about seventy days and was followed by a month without any of the powder inhalation.

Patients were instructed to use their own antispasmodic material as required, but in successful ("much improved") cases the need for this vanished. They were also asked to keep a diary of the number of attacks of spasm and the amount and type of antispasmodic material required during the trial.

Each hydrocortisone capsule contained 15 mg. of the acetate (equivalent to 13.4 mg. of hydrocortisone base), making the daily dose 3 mg. Each prednisolone capsule contained 5 mg., making the daily dose 1 mg.

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Treatment	No. and sex of patients	Age (yr.)	Duration of asthma (yr.)
Hydrocortisone	24 (8M., 16F)	16–63 (av. 42)	0.5–45 (av. 13)
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Blank	13 (6M., 7F)	25–66 (av. 45.5)	3–32 (av. 14)
Total	44 (17M., 27F)	16–66 (av. 43)	0.5–45 (av. 13)

TABLE II—CLASSIFIED RESULTS

Result	Hydrocortisone	Prednisolone	Blank
Much improved	13	1	2
Improved	4	—	3
No better	7	6	8
Total	24	7	13

Progress was assessed according to the lessening of attacks in duration and frequency, the lessening of the need for antispasmodic material, and the improvement in health and mobility. The dosage was so small that no side-effects of steroid therapy arose.

Results

The details of our patients are shown in table I. Our results are shown in table II. The cases treated with hydrocortisone are analysed in table III. The details of the successful cases do not materially differ from those of the unsuccessful, the patients tended to be a little younger but more chronic.

The duration of the remissions was precisely similar for the much improved and improved groups, varying from two weeks to four months (average six weeks). 5 patients returned to hydrocortisone inhalations—3 with improvement, 2 without. These latter thought that the material obtained from the chemist was not the same as we had provided.

To assess our results statistically we grouped the much improved and the improved cases together and compared them with the number of failures.

It appears that the hydrocortisone produces significant benefit, the probability that results as good as these should have occurred by chance alone is only 0.028. The number of patients treated with prednisolone is too small to lead to firm conclusions. There is no evidence of improvement over the placebo, but the results are significantly inferior to the hydrocortisone (P=0.029).

Discussion

The dosage of hydrocortisone acetate given by inhalation in our patients was so small that the beneficial effects must have resulted from a local action on the bronchial tree and not to a systemic effect after absorption. This action is presumably similar to that of steroids applied topically in skin diseases. When used in this way in dermatology hydrocortisone is superior to prednisolone (Frank and Stritzler 1955). The reason for this is not clear, but it may explain why there was no significant benefit in our patients treated with prednisolone inhalations. Difference in solubility of the two steroids will not readily explain the different results, because hydrocortisone acetate is said to be insoluble in water, whereas prednisolone is almost insoluble (*British Pharmaceutical Codex 1954* Supplement 1957, pp. 29 and 60). The lack of solubility of hydrocortisone acetate, however, may explain why the powder gave a beneficial effect by inhalation whereas none was demonstrated in our previous trial using a solution of hydrocortisone hemisuccinate. The solution may well have been rapidly absorbed without there being sufficiently long contact between the hydrocortisone and the bronchial mucosa for any beneficial effect to result.

TABLE III—ANALYSIS OF PATIENTS TREATED WITH HYDROCORTISONE

Result	No. and sex of patients	Age (yr.)	Duration of asthma (yr.)
Much improved	13 (4M., 9F.)	16–58 (av. 40.5)	0.5–45 (av. 17)
Improved	4 (1M., 3F.)	35–48 (av. 43)	3–19 (av. 7.5)
No better	7 (3M., 4F.)	21–63 (av. 46)	4–15 (av. 9.5)
Total	24 (8M., 16F.)	16–63 (av. 42)	0.5–45 (av. 13)

Summary and Conclusions

The value of hydrocortisone acetate and prednisolone powder inhalations in the treatment of chronic asthma has been assessed by a blind trial method.

Of 24 patients receiving the hydrocortisone acetate powder 17 were improved or much improved, a statistically significant figure compared with the results obtained in 13 patients with a blank inert powder.

There was no evidence in 7 patients that prednisolone was of any value when used in this way.

In our opinion this simple method of administering hydrocortisone acetate is well worthy of trial in the less severe cases of asthma.

We are grateful to Dr. Avery Cotton, of the Upjohn Company of America, for sending us the material, and to Dr. E. W. Emery, lecturer in medical physics, and Dr. S. W. Stanbury, lecturer in medicine, for their help.

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TIME OF RECURRENCE OR CURE OF TUMOURS IN CHILDHOOD

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Collins et al. (1956) have given theoretical reasons why the period is limited within which a treated neoplasm may recur (the "period of risk"). They showed that this held true in the results with 206 children from several series treated for Wilms' tumour (embryoma). There were no deaths or recurrences after the defined period of risk had ended. Patients surviving after the period of risk could be presumed to be cured according to a definite biological criterion. The existence of such a limit to the time within which treated tumours might recur would be clinically useful, and important in the study of the natural history of neoplasms. The present study was undertaken to see whether the experience with three types of childhood tumours (Wilms' tumour, neuroblastoma, and rhabdomyosarcoma) in a total of 244 children seen in a single institution confirmed the findings of Collins et al.

Method

Determination of the period when recurrence is possible is based on knowledge of the growth-rate of a tumour before treatment and extrapolation of this rate after treatment for a period long enough for even a single cell left behind to regrow to a tumour of diagnosable size. This time after treatment is the "period of risk." The choice of children as subjects for this study follows the ingenious use, by Collins et al, of the results with Wilms' tumour to test their hypothesis The growth-rate of tumours before treatment is not generally known for any group of patients, but in children this rate can be assumed within relatively narrow limits The tumour can have grown only since conception, or later, to reach its particular size at the time of treatment. The continued growth at the same rate of even a single cell for a period equal to that designated by the age of the child at treatment (plus nine months' gestation) would result in a tumour mass at least equal to that originally present at treatment. Therefore, if there is to be a recurrence it should appear before the end of the period of risk, at which time the child will be twice the age (plus nine months) that he was at the time of treatment For example, a child treated at one year of age will reach the end of the period of risk one year and nine months later, or at the age of two years and nine months, a child five years old, at ten years and nine months of age Tumours that develop later than conception, or that increase their growth-rate, would recur well before the end of the period of risk, as defined here Slowing of growth-rate, spontaneously or as a result of treatment, could result in recurrence after the end of the period of risk and would negate the prediction

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Two time-periods were ascertained for each patient (1) the time before treatment (age plus nine months' gestation), and (2) the time after treatment until the first recurrence of the tumour or the last negative follow-up Periods were determined to the nearest month In some patients in whom death followed shortly after the recognised recurrence and early in the period of risk, the time of death was accepted in lieu of fixing exactly the time of recurrence In patients surviving late into the period of risk, the time of recurrence was fixed more exactly by the date of the first objective signs found by radiographic, or, less commonly by clinical, examination A few patients with documented recurrences late in the period of risk survived well beyond the end of the period of risk, sometimes with supplementary or palliative treatment The delayed deaths of these patients did not vitiate the prediction of the time of their recurrences, since they had already shown evidence of recurrence of malignancy within the period of risk.

Patients

Records were found for a total of 244 patients treated at the tumour therapy clinic of the Children's Medical Center, Boston, during the past two decades, for the three types of tumours selected These particular tumours were selected simply because they are common The diagnoses in all patients in this study were confirmed by histological examination In each group the ages of patients ranged from newborn to about 16 years No selection was made as to the mode of therapy

Wilms' tumour—This was diagnosed in 92 patients The treatment was generally that of Gross and Neuhauser (1950) 5 patients were lost to follow-up immediately after hospital discharge while still apparently well, and these were not incorporated in the series Of the 87 remaining patients 27 were alive and without recurrence at the last follow-up and 60 had died or had had recurrences There was objective evidence from biopsy necropsy, or X-ray examination in 58 of the 60, for the presence of recurrent Wilms' tumour 2 other patients died at home of recurrences diagnosed solely on clinical grounds 15 of the patients without recurrences were beyond risk.

Neuroblastoma—126 patients with this diagnosis attended the tumour therapy clinic Nearly all of them received chemotherapy, usually after surgery and radiotherapy, as indicated At the time of the last follow-up, 18 patients were alive, with no evidence of recurrence, and 108 had already had recurrences 14 patients were beyond risk

TABLE I—SUMMARY OF RESULTS IN ALL PATIENTS STUDIED

	Recurrence		No recurrence		Total
	Dead	Alive	Period of risk	Safe period	
Wilms tumour	52	8	12	15	87
Neuroblastoma	102	6	4	14	126
Rhabdomyosarcoma	22	2	3	4	31
Total	176	16	19	33	244

Rhabdomyosarcoma—31 patients with this diagnosis were studied The therapy was the same as that described for the previous group At the time of the last follow-up, 7 were still alive (4 of them beyond risk), and 24 were dead or had recurrences

Results

The overall results are shown in table I Separate graphs have been made for the three different tumours (figs 1–3) The time before treatment (age plus nine months) was graphed against the time after treatment to recurrence or last follow-up for each of the patients A line drawn at 45° through the origin separates the period of risk from the safe period, and all recurrences can be seen to fall wholly within the period of risk. The patients followed long enough to be in the safe period without recurrence are presumambly cured Those with the period of risk, but negative at the last follow-up, are critical cases which should be followed closely until they are beyond risk

Discussion

The results in three of the commonest tumours of childhood confirmed the observations by Collins et al in a heterogeneous collection of 206 cases of Wilms' tumour There were no recurrences after the safe period was reached A single recurrence in the safe period would

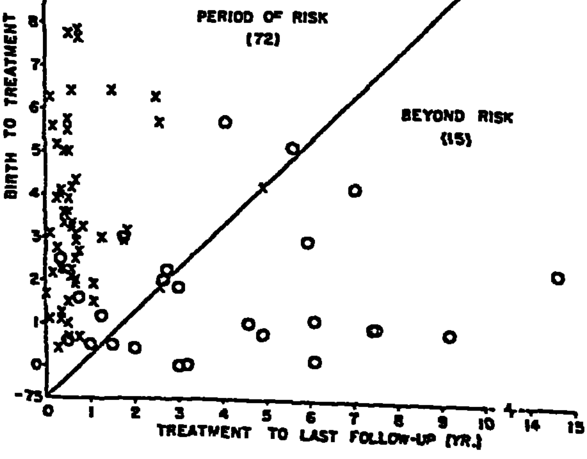

Fig 1—87 cases of Wilms tumour

disprove the thesis of an invariably constant or increasing rate of growth in tumours despite therapy. The results obtained are consistent with this thesis though they do not supply positive proof of it. The qualitative dichotomy of the post-treatment time into two periods—a period of risk and a safe period—is clear and arresting.

There is a highly significant difference in the results during these two periods by the x^2 test, but it is difficult to prove that this distribution did not arise by chance, because all tumours tend to recur early, long before the end of the period of risk. It is possible only to show, as did Collins et al. (1956), that the number of individuals cured by their criterion (i.e., reaching the safe period) was equal to that fraction of the whole group who were dying at a normal rate instead of an accelerated rate (i.e., equal to the "proportion cured," calculated from the statistics of the whole group by the method of Boag [1949]). The essential value of these results, however, is the application of a criterion of cure to an individual. The combined experience with a total of 293 Wilms' tumours, for example, strongly suggests that the criterion of cure discussed here is reliable.

The existence of a biological criterion of cure applicable to individuals treated for neoplasms will have important uses, even if applied *empirically without reference to its theoretical basis.* Even more important issues arise from the theoretical considerations. The criterion was developed from the reasonable assumption that neoplastic cells, like other populations, will tend to grow logarithmically at a constant rate under optimal conditions, so that their number (and therefore their mass) doubles in each interval of time. An interval of time after treatment, equal to that period when the tumour could have existed before treatment, therefore limits the period within which a recognisable tumour would recur. These results provide no direct evidence for the way tumours grow, and only circumstantial evidence for the theory itself. The results are consistent with this theory, since in no instance was a tumour *found to grow more slowly after treatment.* Such exceptions would be of particular interest in guiding tumour therapy.

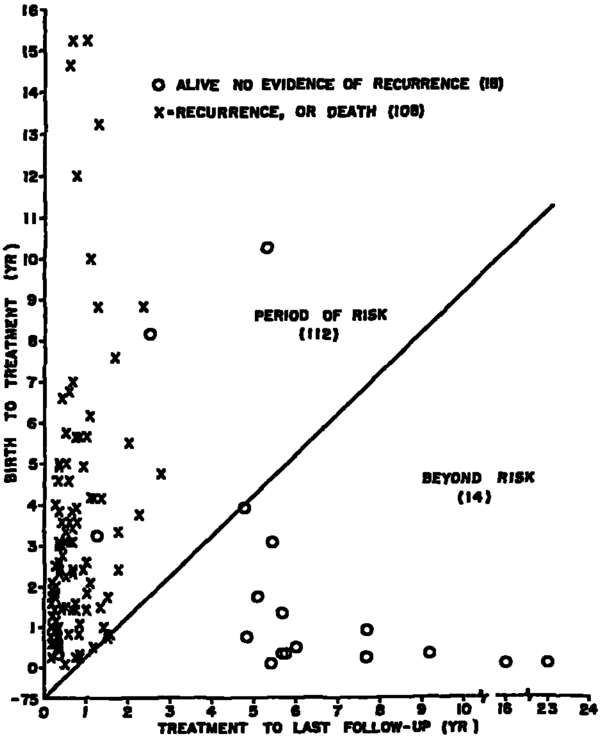

Fig 2.—126 cases of neuroblastoma.

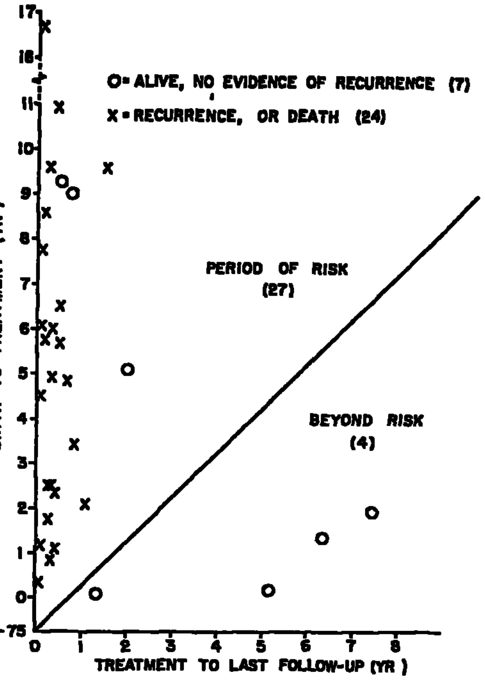

Fig 3.—31 cases of rhabdomyosarcoma.

Positive evidence for the theory may be obtained by the results of longer follow-ups of larger numbers of patients, or by direct determination of tumour growth-rates in individuals of different ages. In either of these ways an important implication of the theory could be tested—viz., that the tumour which grows to a recognisable mass in a young child is growing more rapidly than one attaining a similar mass in an older child. In a series sufficiently large to include late recurrences at each age, it should be possible to show that the disease in younger children usually recurred earlier than in older children. Also, by direct radiological measurement, metastases in young children should be found to grow more rapidly than those in older children. In adults the possible long time-span of tumour growth would prevent significant use of this theory, unless based on actual measurements of growth-rates of the individual tumours.

If the results of this study are accepted, one of the consequences should be the adoption of a sliding time-scale for the follow-up of patients after treatment. Definitive results can be known quickly in young children, but for older children the usual follow-up period should be extended, commensurate with their age at treatment.

Summary

The hypothesis that a treated neoplasm will recur only within a defined period of risk after treatment was tested and confirmed by the results in 244 children with tumours (Wilms' tumour, neuroblastoma, and rhabdomyosarcoma).

All tumour recurrences developed before the end of the period of risk, defined as twice the age at treatment plus nine months.

In 192 cases there was a recurrence. *Of the 52 cases in which there was no evidence of recurrence at the last follow-up, 19 were still within the period of risk. The remaining 33 were beyond risk and therefore could be assumed to be cured.*

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TREATMENT OF UNDULANT FEVER

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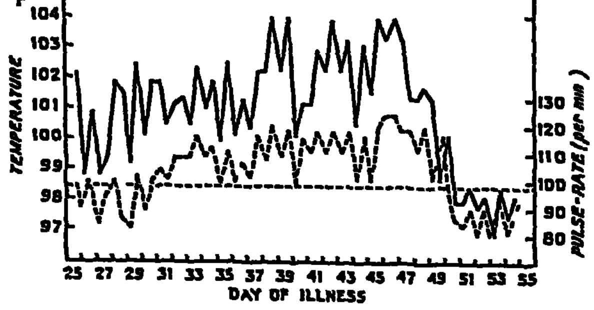
Up to a few months ago we did not have a specific and efficacious antibiotic with which to treat undulant fever Neither streptomycin nor aureomycin, let alone vaccines, gold compounds, &c, was surely therapeutic in this infectious disease, and invariably the end-results, after treating the patients with these antibiotics, were complete failures, because almost constantly the disease recurred Even without complications—e g, spondylitis, which cripples for life—undulant fever used to last a year or two

Some months ago a new antibiotic, 'Cathomycin', was supplied to us for treating infections resistant to penicillin For various reasons and of my own initiative I used it to treat patients with undulant fever After treating the first few cases, I realised that cathomycin is a specific effective antibiotic in undulant fever Up to now we have treated 26 patients, who have been discharged from hospital completely cured, and not one has had a recurrence Of the 26 patients treated 20 had produced a positive blood-culture on admission and the remaining 6 had a positive agglutination test. Only the 20 patients with a positive blood-culture are discussed here Their details are shown in the accompanying table We treated the patients only when the undulant fever was at its height

The constant effect of cathomycin was remarkable (see figure) During the first five days' treatment no change is apparent, the pyrexia continues as before, and the symptoms remain just the same, but almost always on the fifth day the pyrexia resolves by crisis and all the symptoms (headache, insomnia, articular pain, anorexia, sweating, &c) disappear Splenomegaly also disappears, and by the end of the treatment the spleen has returned to its normal size and shape, no matter how large it was None of the patients relapsed

Dosage—A capsule containing 0 25 gs was given four-hourly until the day after the crisis (usually the sixth day) and then six-hourly for nine days to a total of 18 g Of course this dosage applies only to adults



Typical chart of temperature and pulse-rate in undulant fever before and during treatment with cathomycin.

ANALYSIS OF CASES OF UNDULANT FEVER AND TREATMENT

Case no	Sex	Age (yr)	Duration of disease before treatment	No of days' treatment before crisis	Temperature at beginning of treatment (°F)	Total dose of cathomycin (g)
1	F	35	2 mos	5	98·6—100·4	14·0
2	F	36	1 month	6	98 6— 99 5	12·0
3	M	7	1 month	5	100 4—102 2	13 5
4	M	33	3 mos	5	99 5—102 2	27·0
5	M	52	1½ mos.	5	99 0—102 2	17 5
6	M	31	2 weeks	10	100·4—104 0	20 0
7	M	11	2 weeks	6	101 5—103 6	13 5
8	F	26	10 days	6	100 4—101 3	13 75
9	M	30	3 weeks	5	99 5—100 4	17 5
10	M	27	1 month	5	100 4—102 2	20 5
11	M	30	1 month	6	101 3—103 1	16 0
12	M	17	2 weeks	4	100·4—102 2	18 7
13	M	45	2 mos	5	100 4—103 1	20 0
14	M	52	2 weeks	5	99 5—102 2	20·0
15	M	45	2 mos	5	99 1—103 1	18·0
16	M	57	1 yr	4	98 6—100 4	18 0
17	M	19	3 mos	5	99 5—100 4	18·0
18	F	7	1 month	5	100·4—101 3	12 5
19	F	32	1 month	5	100 4—101·4	18 0
20	M	18	2 mos	5	100 0—101 3	18 0

Laboratory Findings—On the third day of treatment liver-function tests (Kunkel's, Maclagan's, Hanger's, and Wuhrmann's), which were frequently made, were always negative The leucopenia, which sometimes was very severe, rapidly disappeared Anæmia, which also is common in undulant fever, gradually returned to normal The platelet count was usually normal and did not vary in any way during the treatment No organic alterations were found

Psychology—The patient's state of mind was much improved as soon as his temperature had returned to normal Many of the chronic patients who had become pessimistic became cheerful and self-confident again after losing their fever and pain

Side-effects—A quarter of the patients manifested intolerance of cathomycin

Case 10 (see table) during the first three days of treatment had hyperchlorhydria, which was relieved by alkalis without stopping the treatment.

Case 5 had a generalised urticarial rash, with pyrexia up to 104°F, but with the patient's cooperation we did not withhold cathomycin but gave him the full fifteen days' treatment. On the day that he stopped having cathomycin his temperature returned to normal, two days later the exanthema disappeared, and he was discharged completely cured

Case 6 was treated for ten days On the eighth day an urticarial eruption appeared, causing him so much discomfort that we had to withhold cathomycin for two days, during which time the rash disappeared We gave him cathomycin again, but after the third capsule the exanthema reappeared, accompanied by pyrexia up to 103°F Since the patient asked us not to stop the treatment, we carried on for the remaining four days Two days later all his ailments disappeared, and on the third day he was discharged home completely cured

In case 8 urticaria appeared on the eighth day of treatment, but the treatment was continued to the tenth day, when we had to withhold cathomycin because the patient could no longer bear the itching caused by the rash. Four days later, when the urticarial rash had subsided, we continued the treatment, but at the third capsule the exanthema reappeared, this time with such severe symptoms that we had to abandon treatment with cathomycin Although the patient had had only 10 days' treatment he was definitely cured, and three days later he was discharged

So far the urticarial eruption has been the only inconvenience caused by cathomycin

Conclusion

In all our knowledge and experience of undulant fever we have never seen or achieved such good results This infectious disease is completely cured in about five days without a single recurrence For these reasons we regard cathomycin as an efficacious and specific antibiotic to be introduced and used in the treatment of undulant fever If our findings are confirmed, as we feel sure they must be, we may consider the battle against brucellosis to have been won

HÆMOGLOBIN-H TRAIT IN A NEPALESE GURKHA WOMAN

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Since Pauling et al (1949) described the electrophoretic properties of sickle-cell hæmoglobin, several other types of abnormal adult human hæmoglobin have been detected Of these, hæmoglobins S, C, D, E, and G have a mobility lower than that of normal adult hæmoglobin, while hæmoglobins I, J, K, and H, that of Cabannes et al (1955), and the Liberian 2 of Robinson et al (1956) have a mobility higher than that of normal adult hæmoglobin Hæmoglobin H differs from all the other abnormal hæmoglobins in having an anodal mobility at pH 6 5, the other *hæmoglobins having a cathodal mobility at this* reaction

Hæmoglobin H was described simultaneously in two Chinese siblings settled in America by Rigas et al (1955) (1956) and in seven Greeks by Gouttas et al (1955) These patients had hypochromic microcytic anæmia resistant to therapy, with splenomegaly, and with a blood-picture very like that of thalassæmia but accompanied by the presence of hæmoglobin H in the erythrocytes Hæmoglobin-H trait has also been found in Thais (Minnich etal 1956), in Indochinese in Indonesia (Lie-Injo Luan Eng et al 1957), in Filipinos (Motulsky 1956), in Singapore Chinese (Vella 1957), in a Greek Cypriot (Ager and Lehmann 1957), in a Malay (Lehmann and Singh 1957), and in a Trans-Jordanian Arab (White et al 1956)

The Nepalese Gurkha woman described here presented *with a severe hypochromic anæmia and splenomegaly* As the anæmia responded to treatment, she was held to have a nutritional iron deficiency such as is commonly found in her race Additional support was given to this belief when the anæmia relapsed on her becoming pregnant and when she was found to have ankylostomiasis The anæmia now responded only partially, despite large doses of parenteral iron When this ultimate lack of response to treatment was recognised, a thalassæmia-like anæmia was considered, and electrophoresis was carried out This revealed the presence of hæmoglobin H

Electrophoresis was done on *Whatman filter paper (3 MM)* between glass plates measuring 14 in × 10 in × 0 25 in, treated with silicone stopcock grease, and clamped with four Waverley clips (no 3), using veronal buffer pH 8 8 (ionic strength 0 06) and citrate buffer pH 6 5 (ionic strength 0 05) Runs were made in a refrigerator, at about 5°C, at 360V for five or six hours (Chernoff 1955) *Alkali-*resistant hæmoglobin was measured by the Chernoff technique (Chernoff 1955) Inclusion bodies were demonstrated by supravital staining with brilliant cresyl blue (Gouttas et al 1955)

Case-report

A Nepalese woman, aged 24, complained of fever soon after arriving in Malaya from India in April, 1956 She was admitted to the British Military Hospital, Singapore, with a temperature of 99°F, pale mucosæ, and slight icterus Her liver was palpable to one fingerbreadth below the costal margin and a firm non-tender spleen was palpable to two fingerbreadths Laboratory investigations showed red cells 3,050,000 per c mm, Hb 6 8 g per 100 ml, white cells 5100 per c mm (polymorphs 57%, lymphocytes 35%, monocytes 5%, eosinophils 3%) *Malarial parasites were absent, a blood-film showed* poorly filled red cells with considerable anisocytosis and poikilocytosis Serum-bilirubin 0 4 mg per 100 ml, no urobilinogen in urine Lung fields clear on radiography

Fig 1—Peripheral blood smear

Treatment and Progress

She was treated with oral iron, and in three weeks her hæmoglobin increased to 8 9 g per 100 ml, and red cells to 3,090,000 per c mm A blood-film showed active regeneration She was discharged from hospital with a diagnosis of iron-deficiency anæmia

She was readmitted in November, 1956, with symptoms of anæmia and was now twenty-two weeks pregnant Apart from the pregnant uterus, the clinical findings were essentially the same as at her previous admission Hb 5 2 g per 100 ml, blood-film showed hypochromic microcytic red cells but no target cells, white-cell count normal Stools contained ova of *Ancylostoma duodenale*

She was treated with tetrachlorethylene and with 'Imferon' The anæmia persisted, but the hæmoglobin gradually rose to 9 6 g per 100 ml before she gave birth on March 4, 1957, to a premature female baby weighing 3 lb 13 oz

She was first seen by one of us (M C B) a month after delivery On examination she had the typical mongoloid features and short stature of her race The mucosæ were pale and fingernails and tongue normal The liver and spleen were palpable to the same extent as before She had no abnormal physical signs in the nervous, respiratory, and cardiovascular systems, apart from an apical systolic murmur

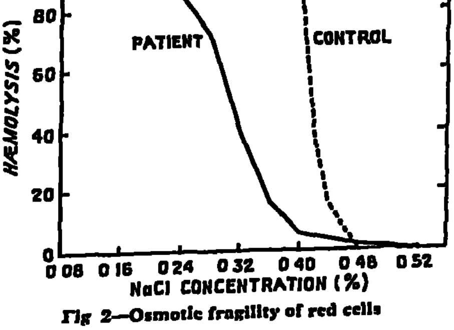

Fig 2—Osmotic fragility of red cells

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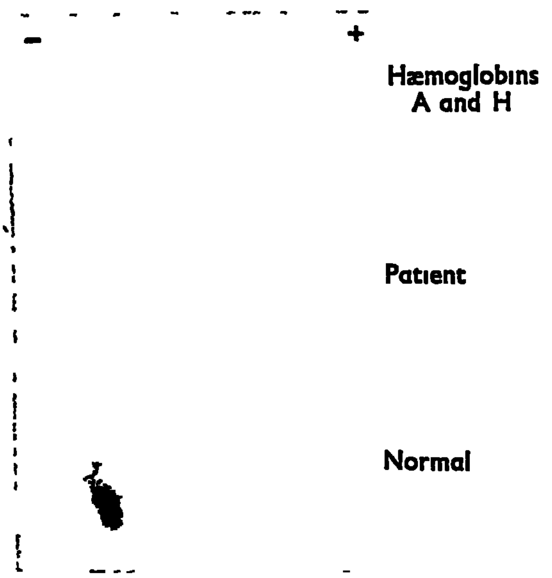

Fig. 3—Electrophoresis pattern (pH 6·5) of hæmoglobin solutions A and H standards, patient, and normal.

Investigations

Red cells 5,600,000 per c.mm., Hb 11·5 g. per 100 ml., packed cell volume 37%, mean corpuscular volume 66 c μ, mean corpuscular hæmoglobin 21 μμ, mean corpuscular hæmoglobin concentration 31%, a stained smear showed considerable anisocytosis and poikilocytosis (fig. 1). No target cells were seen. Sickling could not be induced. Reticulocytes 5%. White-cell count normal. The osmotic fragility curve (fig. 2) showed increased resistance to hypotonic saline solution, there was 5% hæmolysis in 0·4% sodium chloride and 60% in 0·3% sodium chloride. Bone-marrow was very cellular and showed normoblastic erythroid hyperplasia, the myeloid/erythroid ratio being 1/1.

Electrophoresis gave the results shown in fig. 3. Hæmoglobin A 70%, hæmoglobin H 30%, alkali-resistant hæmoglobin 0%.

Supravital staining of peripheral blood with brilliant cresyl blue revealed inclusion bodies in 40% of the red cells (fig. 4). In bone-marrow stained by the same technique 1% of the red cells contained intracellular inclusions. The inclusion bodies were not seen in any nucleated red-cell precursors.

Serum-bilirubin 1·0 mg. per 100 ml., liver-function tests normal. Serum-albumin 4·4 g. per 100 ml., serum-globulin 1·85 g. per 100 ml. Urine no urobilinogen detected. Blood-group O, rhesus-positive. Blood Wasserman reaction negative. Coombs antiglobulin test negative. A test-meal showed acid secretion, which was confirmed by a positive 'Diagnex' test.

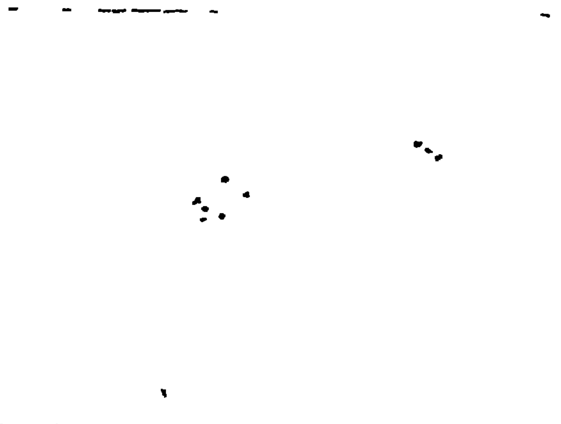

Fig. 4—Peripheral blood stained supravitally with brilliant cresyl blue to show intraerythrocytic inclusion bodies.

Uropepsinogen excretion 57 units an hour. Serum-iron 205 μg per 100 ml. Stool no ova of *Ancylostoma duodenale* found in six specimens, no occult blood.

Radiographs of the skull showed an area in which the diploic space was enlarged, but no spiculation was evident. Radiographs of the hands were normal.

Family History

The patient is the youngest of a family of five. Her parents, brother, and three sisters are alive and well but not available for study. Her husband is quite fit and not anæmic, on electrophoresis his hæmoglobin was normal, alkali-resistant hæmoglobin 0%. Her daughter at the age of 6 months was normal for her age.

3,870,000 per c.mm., Hb 9·9 g. per 100 ml. Blood-film slightly hypochromic but otherwise normal. No intraerythrocytic inclusions bodies. Reticulocytes 1·6%, white-cell count normal. Electrophoresis at 5 weeks hæmoglobins A+F, alkali-resistant hæmoglobin 60%, at 10 weeks hæmoglobins A+F, alkali-resistant hæmoglobin 40%, at 16 weeks hæmoglobins A+F, alkali-resistant hæmoglobin 17%, at 6 months hæmoglobin A, alkali-resistant hæmoglobin 3%.

Discussion

Hæmoglobin H is the only known abnormal hæmoglobin which in the heterozygous state produces a clinical syndrome of mild anæmia resistant to therapy and associated with splenomegaly and little if any hæmolysis. The diagnosis is possible only on electrophoresis at both an alkaline and a slightly acid reaction, though supravital staining with brilliant cresyl blue will show up intraerythrocytic inclusion bodies of denatured hæmoglobin H on to which the cresyl blue has been adsorbed. It is not yet certain whether these intraerythrocytic inclusion bodies are associated only with hæmoglobin H.

Minnich et al. (1956) have reported inclusion bodies in a case of hæmoglobin-E thalassæmia in Thailand. One of us (F. V.) has shown that both hæmoglobins E and H can be precipitated from solution by adding brilliant cresyl blue or metabisulphite, whereas hæmoglobins A and F are more resistant to precipitation (Vella 1957). Our inability to demonstrate inclusion bodies in the red-cell precursors in the bone-marrow, and the small number of red cells containing inclusion bodies seen there, suggest that a physicochemical change in the hæmoglobin with ageing of the red cell may lead to its precipitation with brilliant cresyl blue. This might explain the marked variability in the quantity and density of inclusion bodies seen in red cells in the peripheral blood.

The peripheral blood-picture in persons with hæmoglobin-H trait has been described as indistinguishable from that in Cooley's anæmia. In fact, these cases are usually classed as thalassæmia syndrome until electrophoresis is done. Motulsky (1956) has concluded:

> "In the present state of our knowledge, the demonstration of hæmoglobin H apparently signifies the simultaneous presence of Thalassæmia. Thalassæmia-Hæmoglobin H Disease therefore may be considered a variant of Thalassæmia in which the Thalassæmia gene in a yet unknown manner activates the expression of hæmoglobin H."

Apparently the expression of the hæmoglobin-H gene may also be enhanced by the simultaneous presence of a gene for another abnormal hæmoglobin (Vella and Wells 1957).

Production of hæmoglobin H is controlled by a recessive gene, so far only three cases are known in which people with hæmoglobin H have produced offspring. Rigas et al. (1956) found the child of one of their patients to exhibit an iron-resistant anæmia with target cells and microcytosis but no splenomegaly and no demonstrably abnormal hæmoglobin, and they diagnosed thalassæmia minor. However, one of the patients of Gouttas et al.

(1955) is married to a clinically and hæmatologically normal partner and has produced a child known to carry hæmoglobin H Our own patient's daughter showed no abnormality of hæmoglobin at the age of 6 months No abnormal hæmoglobins have yet been detected before the 12th week of life (Lie-Injo Luan Eng 1956)

As no siblings or parents of this patient were available for study, the relation of the hæmoglobin-H recessive gene to the gene(s) responsible for the thalassæmia could not be ascertained in this case

The initial response of this patient's anæmia to therapy and her relapse on becoming pregnant are attributed to a concomitant deficiency of iron The failure of the hæmoglobin to rise to a normal level once the ankylostomiasis had been treated and the iron deficiency had been made good, is characteristic of the thalassæmia-like anæmias and agrees with the descriptions published of hæmoglobin-H trait Once the nature of the anæmia was appreciated, further attempts at "treatment" were discontinued The patient remains well and symptom-free, leading an active life with a hæmoglobin of between 8 0 and 11 0 g per 100 ml

Summary

A case is described of a Nepalese Gurkha woman, aged 24, with hypochromic anæmia, splenomegaly, and ankylostomiasis, partially responding to treatment

On electrophoresis hæmoglobin H was found to constitute 30% of the total hæmoglobin

The patient's daughter, aged 6 months, has no abnormal hæmoglobin and is clinically normal

We are grateful to the Director-General of Army Medical Services for permission to publish, and to Lieut -Colonel T E Field, R A M C, and the staff of the Pathology Laboratory, FARELF, for the hæmatological and biochemical investigations

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ANAPHYLAXIS AFTER ORAL SULPHADIAZINE

TWO REACTIONS IN THE SAME PATIENT WITHIN EIGHT DAYS

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Case-report

A lady schoolteacher, aged 41, had had sore throats for about a year, and four months before admission her doctor had given her a course of sulphadiazine

Eight days before admission she had a sore throat, and her doctor prescribed sulphadiazine as 4 tabs (2 g) stat, and 2 tabs (1 g) four-hourly She took 4 tablets, and within half an hour she was "lathered" in sweat, but felt "cold and shivery" She had a tickling cough, but no breathlessness or wheezing, and noted itching white urticarial weals "like large heat lumps up to an inch in diameter" appearing on arms, spreading to face (which "felt tight and prickly"), and then to rest of the body The urticaria was followed by generalised erythema within an hour Her mouth was swollen and her tongue stiff, and her skin felt to be burning furiously She vomited once, but had no diarrhœa or loss of consciousness She decided not to take the tablets as prescribed during the rest of that day

Next morning the redness had disappeared, but as her throat was still sore she took 2 tablets of sulphadiazine and continued to do so four-hourly for three days without ill effect Her throat was then much improved and she felt better and ceased to take the tablets Thirty-six hours before admission the "bad throat" recurred

At 11 30 A M on the day of admission she took 2 tablets of sulphadiazine Within half an hour she started sweating profusely and felt cold Itching urticarial areas 1½ in in diameter appeared on her arms and spread all over her body, followed by redness within half an hour At this stage she had an irritating cough with slight wheezing and breathlessness Then she had violent cramp-like pains in the epigastrium, passing into the lower abdomen in less than ten minutes She twice vomited greenish-yellow fluid with coincidental severe exhausting diarrhœa, when she felt very weak and ill, and "did not care whether she lived or died" He sister said her colour was greyish purple, with blue lips, and she was groaning and shivering as she tried to sit on the commode Her eyes were staring and then deviated upwards, followed by loss of consciousness for a few minutes with convulsive movements of arms and legs Gradually consciousness returned Her doctor arrived shortly after this and noted that she was profoundly shocked and pulseless She vomited once in the ambulance

She had no history of allergic disease, but had had deep X-ray treatment for thyrotoxicosis in 1940 A sister had asthma

Condition on Admission

Her eyes were staring and her conjunctivæ suffused and bloodshot Face ashen grey with cyanosis of lips She appeared too weak to talk, but was trembling enough to cause the bed to shake Her hands and feet were cold and blue On her trunk, limbs, back of neck, and scalp were urticaria (with interlacing pseudopodia) and bright erythematous areas Temperature 97 6°F The pulse was not palpable, and the blood-pressure (B P) irrecordable The heart-rate (at auscultation) was 138 a minute and the respiratory rate 38 There was no bronchospasm The tonsils were large and injected No other gross abnormalities were found

Course

10 minims of adrenaline 1/1000 solution was given subcutaneously at 2 P M Within ten minutes, the trembling had

ceased, but retching and diarrhœa continued intermittently. She gradually improved during the afternoon, another 3 minims of adrenaline was given at 5 P.M. Next morning her pulse-rate was 90 a minute and B.P. 120/80 mm. Hg, there were still occasional urticarial weals on her body. A throat swab revealed *Staphylococcus aureus*.

Discussion

Of special interest are the rapidity of onset of symptoms after administration by mouths and two episodes separated by freedom from reactions while taking the drug.

Dale (1920) postulated a latent period of twelve to fourteen days after the initial exposure to the foreign substance, during this time antibody is formed and becomes fixed in the cells. When the foreign substance again reaches the circulation, any plasma-antibody is precipitated, the excess foreign agent reacts with antibody within the cells to liberate histamine and other substances, which produce anaphylactic manifestations.

Landsteiner (1936) observed that simple chemical substances could combine with proteins in the body to form a modified protein antigen. A molecule containing a benzene-ring nucleus with an $-NH_2$ group attached, or a molecule with a pyrimidine nucleus, is highly antigenic. Sulphadiazine contains both a benzene ring with an $-NH_2$ group, and a pyrimidine group.

The time intervals in this case accord with Dale's hypothesis: a sensitising dose four months before admission, a reaction eight days before, then freedom from symptoms for three days while on the drug, when the antibody in cells had been neutralised, and then a reaction on the day of admission, when the antibody here had again built up in the tissue cells.

My thanks are due to Prof. P. J. Moir for kind permission to publish this report.

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PERIURETERIC FIBROSIS

HAROLD PARK
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SENIOR SURGICAL REGISTRAR, KING'S COLLEGE HOSPITAL, LONDON, S.E.5

PERIURETERIC fibrosis (*Lancet* 1957) is probably not so uncommon as the paucity of published reports thereof suggests. We describe here a further case, in which, as is characteristic of this condition, we followed many false trails before we stumbled on the correct diagnosis.

Case-report

A man, aged 39, was admitted to the medical wards of the Royal Sussex County Hospital on Feb. 25, 1957, because of repeated attacks of vomiting accompanied by a girdle-type pain starting in both loins and radiating to the epigastrium, where it persisted in attacks lasting five hours. For some months he had had vague abdominal aching centred in the region of his umbilicus, and he had lost about 2 st. in weight and felt ill. The pain was unrelated to food, and there had been no disturbance of micturition.

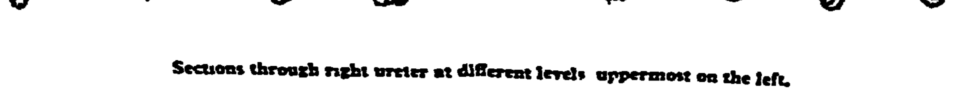
On admission he was thin, ill-looking, and apprehensive but did not present any abnormal physical signs. In view of his nausea, vomiting, and epigastric pain attention was at first focused on his alimentary tract. A barium meal showed no abnormality other than partial loss of mobility of the terminal ileum, this last was thought to be due to adhesions. Examination of the blood showed microcytic anæmia (Hb 11 g. per 100 ml.), white cells 7900 per c.mm., but a surprisingly high blood-urea level (138 mg. per 100 ml.) and serum-potassium level (26.3 mg. per 100 ml.), all the other serum-electrolyte levels being normal. The urine was sterile, with a few red cells and white cells present in the centrifugal deposit. Intravenous pyelography showed a non-functioning right kidney and some early dilatation of the calyces in the left kidney. The fact that the left ureter persistently lay near the midline did not at first attract attention.

Cystoscopy on March 18, 1957, showed a normal bladder, but a catheter could not be passed more than 5 cm. up the right ureter. A further attempt three days later also failed. During this first month the patient's general condition improved spontaneously, as did his blood chemistry, the blood-urea level reaching 264 mg. per 100 ml. before falling to normal levels by the end of March. This spontaneous recovery of renal function, which we now know to be characteristic of periureteric fibrosis, was not appreciated at the time.

Exploration of the right kidney was done on March 28 through an anterolateral approach with a view to either a plastic operation for hydronephrosis or a nephrectomy. Great difficulty was experienced in finding the ureter. For a time what proved to be the dilated upper end of the ureter was taken to be the renal vein as it ran transversely before disappearing into a large firm pinkish mass, which involved all the retroperitoneal structures from the level of the body of L2 vertebra to that of L5 vertebra. The ureter, identified distally, resembled a vas deferens in its calibre and consistence, and was freed down to the pelvic brim. No peristalsis was seen. The mass was thought to be neoplastic, and the changes in the ureter to be due to neoplastic infiltration. Nephro-ureterectomy was then done. Recovery was uneventful.

Pathology.—The kidney measured 11 × 6.5 × 4 cm. and weighed 186 g., with 14 cm. of ureter attached. There was mild hydronephrosis, with dilatation of the upper part of the ureter, but the lower 6 cm. of ureter was contracted and hard, with somewhat the texture of a vas deferens. In the narrowed segment of ureter the lumen was narrowed to a slit but retained normal epithelium. In the wall, lying outside the muscularis but partly infiltrating it was a plaque of young fibrous tissue with patchy lymphoid infiltration, chiefly perivascular. One small arteriole showed what appeared to be subacute arteritis with cellular infiltration of the media and proliferation of the endothelium. The kidney had a distinct zone of lymphoid infiltration at the outer edge of the cortex, with focal lymphoid infiltration, again chiefly perivascular, scattered elsewhere. There were less arteriolar hyalinisation and more round-cell infiltration than are usual in pyelonephritis. This condition affected the renal parenchyma as well as the ureter, and could only be called "inflammatory" by using this word in a very wide sense. Histologically it was more like temporal arteritis or a collagen disease. The appearances resembled those described by Raper (1955) for periureteric fibrosis, except that there was no calcification (see figure).

Prognosis.—It was now appreciated that the prognosis was good, provided that complete ureteric obstruction did not develop on the left side by involvement in this inflammatory mass. The left ureter was already displaced medially,



Sections through right ureter at different levels, uppermost on the left.

(1955) is married to a clinically and hæmatologically normal partner and has produced a child known to carry hæmoglobin H Our own patient's daughter showed no abnormality of hæmoglobin at the age of 6 months No abnormal hæmoglobins have yet been detected before the 12th week of life (Lie-Injo Luan Eng 1956)

As no siblings or parents of this patient were available for study, the relation of the hæmoglobin-H recessive gene to the gene(s) responsible for the thalassæmia could not be ascertained in this case

The initial response of this patient's anæmia to therapy and her relapse on becoming pregnant are attributed to a concomitant deficiency of iron The failure of the hæmoglobin to rise to a normal level once the ankylostomiasis had been treated and the iron deficiency had been made good, is characteristic of the thalassæmia-like anæmias and agrees with the descriptions published of hæmoglobin-H trait Once the nature of the anæmia was appreciated, further attempts at "treatment" were discontinued The patient remains well and symptom-free, leading an active life with a hæmoglobin of between 8 0 and 11 0 g per 100 ml

Summary

A case is described of a Nepalese Gurkha woman, aged 24, with hypochromic anæmia, splenomegaly, and ankylostomiasis, partially responding to treatment

On electrophoresis hæmoglobin H was found to constitute 30% of the total hæmoglobin

The patient's daughter, aged 6 months, has no abnormal hæmoglobin and is clinically normal

We are grateful to the Director-General of Army Medical Services for permission to publish, and to Lieut -Colonel T E Field, R A M C, and the staff of the Pathology Laboratory, FARELF, for the hæmatological and biochemical investigations

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Reviews of Books

Medical History of the Second World War

Army Medical Services Campaigns Vol ii F A E CREW, F R S H M Stationery Office 1957 Pp 537 84s

THE second volume in this series has the same plan and the eminent virtues of the first [1] Its subjects are the defeats at Hong Kong and in Malaya and the second (and victorious) phase of the battles in North Africa There is also an account of the health of our subarctic garrisons and—probably of the most general interest—a detailed study of the medical aspects of captivity in Japanese hands

In those years we went where we were sent, did as best we could, and—quite often—were sure that we could have done better for our patients and for ourselves if we had had the ordering of affairs in our own hands Fifteen years later it is more profitable to forget pompous authority, supplies ill-chosen, late in arrival, or non-existent, the weeks of empty idleness, and the days and nights of endless and sometimes useless toil If read between the lines this book makes no effort to conceal failure or incompetence, but, without bombast, it shows that there was far more to praise than to blame in the direction of the Army Medical Services For everyone from the Director-General to the battalion medical officer every new campaign is to some extent a leap in the dark Plans must be made, men must be trained, and stores assembled at home the Army Medical Department has no infallible soothsayer to supplement inadequate intelligence or anticipation The personnel are not what A M D 1 would choose but what they have in hand The good soldier is he who can make the best use of all these wherever he finds himself, and, in retrospect, the job was done well far more often than badly The heroes of this book are the A D M S, D D M S, and D M S who faced and solved so many problems new to them and barely mentioned, we would guess, in the scholarly peace of Millbank They planned, devised, begged, cajoled, and improvised with two ends in view—to maintain the health of the fighting Army and to succour the wounded as best they could

There are two lessons to be learned—or relearned First, no administrator who is not a doctor can have the flexible pragmatic outlook needed to employ slender resources to the most profitable end, and there can be no better evidence than this book that the professional direction of the Army Medical Services must be maintained The second lesson is not for the professional soldier only and may be the more urgent By 1939 the lessons of 1918 had been forgotten, if there is another war those of 1945 may have to be learned again at dreadful cost Those responsible for the planning of civil defence will be neglecting their duties if they do not read these volumes thoughtfully and often

Artificial Limbs

LEON GILLIS, M B E, M B, F R C S, consultant orthopædic surgeon to Queen Mary's Hospital, Roehampton, East Ham Memorial Hospital, and St John s Hospital, Battersea London Pitman Medical Publishing Co 1957 Pp 449 £15

Ultima ratio regum ran the inscription about the mouths of Louis XV's cannon—"the last argument of kings" "The last argument of orthopædic surgeons" might once have been engraved on the blade of an amputation knife, but today it would not ring true, for the view is now well established that amputation marks not the end but the beginning of a phase of treatment Since 1948 almost every patient in this country who has undergone amputation—there are a few residential stipulations—has been entitled not only to an artificial limb (and a spare duplicate) but also to the help of a fitting service prepared to advise and train him in its use

Mr Gillis points out that we can justifiably take pride in the fact that Great Britain has led the way in establishing such an organisation But little has been published about its activities, materials, and techniques, and his new book, based on his experience at Roehampton, fills this gap

The work, which is complementary to Mr Gillis's earlier monograph on amputation, is in three sections one concerned with measuring the patient for an artificial limb and the fitting of it, another with the construction of the prostheses, and a third with methods of reablement No better survey of British limb-fitting practice, and of tried and tested procedures, could be wished for The surgeon who studies it will find that he can do much to bridge the gap that still sometimes exists between the surgical ward and the limb-fitting centre

Livingstone, the Doctor

MICHAEL GELFAND, O B E, M D, F R C P Oxford Basil Blackwell 1957 Pp 333 42s

A GOOD account of David Livingstone's journeys is always attractive reading, and in some respects Dr Gelfand's is even more interesting to the medical reader than earlier ones have been Its maps are particularly good, and emphasis is laid on the medical side of Livingstone's work, which was considerable and fascinating His medical observations are some of the earliest records on the diseases of Africa He was an accurate observer, who had to rely on the simplest aids to diagnosis He regretted that he had not been able to do necropsies "No inspection of the body is allowed by their people, and the place of sepulchre is carefully concealed I had to rest satisfied with conjecture"

Livingstone observed for the first time the association between relapsing fever and the bite of a tick, one of the earliest records of a disease transmitted by an insect He gave an excellent account of tropical ulcer, a common and very disabling condition at that time, and he probably was one of the first to describe in Africa the boils produced by the maggot fly Two years later he recorded the presence of an insect (one of the filarial worms) in the aqueous humour of the eye of one of his men And, above all, he made notable contributions to the study of malaria

Hewer's Textbook of Histology (7th ed London William Heinemann 1957 Pp 438 27s 6d)—Dr C L Foster has extensively revised the sections describing the cell, the connective tissues, the liver and the pituitary, but the other chapters are virtually the same as in the sixth edition Some new illustrations have been included to supplement the many existing photomicrographs and line drawings The inclusion of additional figures, without altering the numbering, has necessitated the rather cumbersome use of letters in addition to numbers to designate the new illustrations Readers may be disappointed to find no mention of sex-chromatin, nucleic acids, or "spreading factors", and no more than a passing reference to amorphous intercellular substance The very useful appendix on histological methods might well have included an elementary description of electron, phase-contrast, and ultraviolet microscopes The special virtue of this work remains that the text is concise, clear, and covers the subject adequately, it is very well illustrated, and stress is laid on the relation of structure to function and the dynamic aspects of histology

British Encyclopædia of Medical Practice (2nd ed London Butterworth 1957) *Cumulative Supplement* (Pp 308 35s) *Medical Progress* (Pp 339 37s 6d) (The two together cost 67s 6d)—The *Supplement* is a series of addenda to the *Encyclopædia*, designed to bring it up to date with information which "concerns knowledge of proved value, and neither controversial nor doubtful material is included" This year the *Supplement* has increased its size more than its price The companion volume contains a series of articles reviewing advances in all branches of medicine, and selected abstracts, its material is newer but more controversial

Lewis's Medical and Scientific Lending Library—The new edition of the catalogue of this library, revised to December, 1956, may now be had from H K Lewis & Co, Ltd, P O Box 66, 136, Gower Street, London, W C 1 The price is £1 5s to library subscribers and £2 2s to non-subscribers

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[1] See *Lancet*, 1956, ii, 824

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See Lancet, July 22, 1899, p. 219

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See Lancet, May 7, 1932, p. 992

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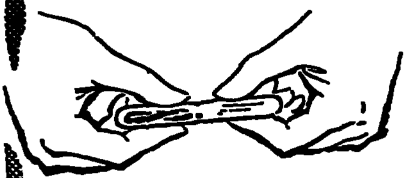

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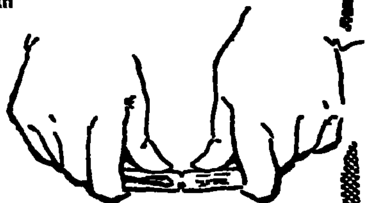

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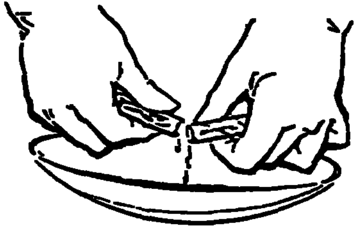

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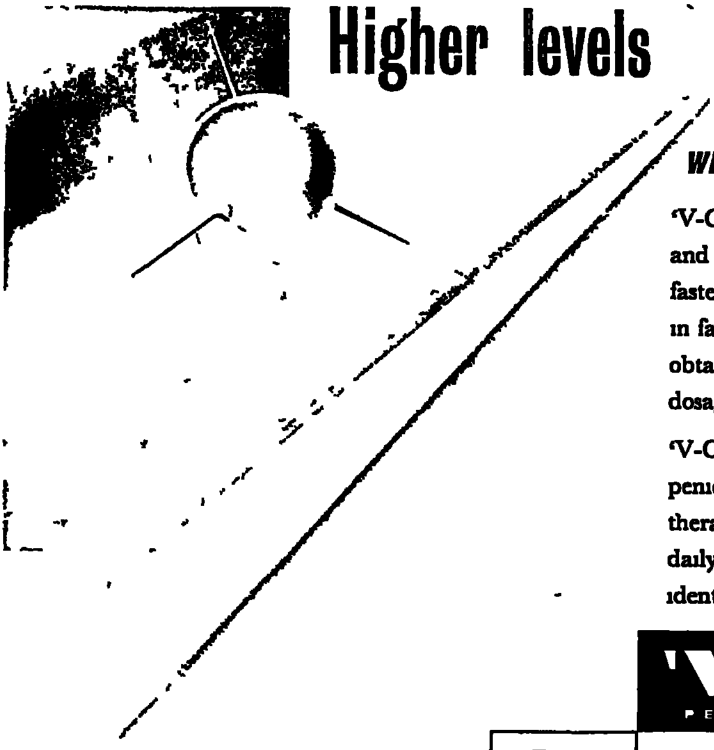

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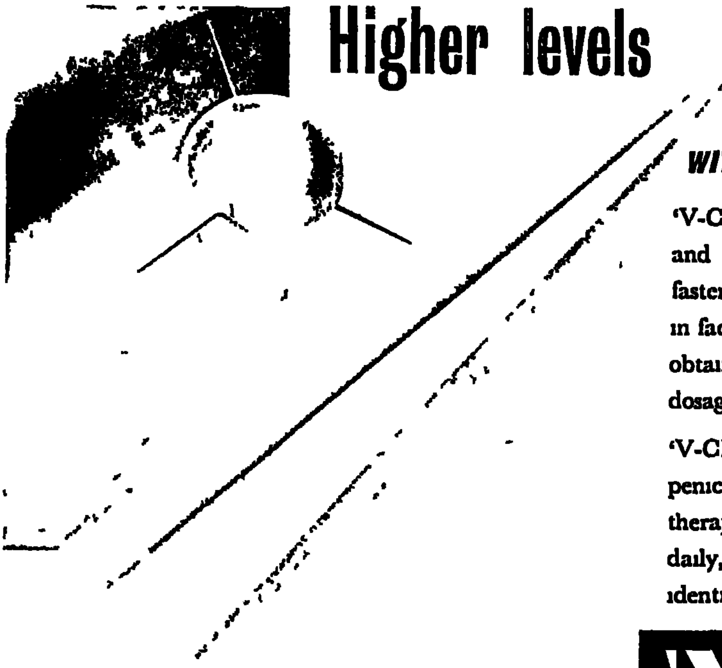

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THE LANCET
LONDON 25 JANUARY 1958

Diabetic Arterial Disease

IN this century of medical revolutions none has been more profound than that affecting diabetes mellitus, for its treatment has been greatly improved and our concept of the disease radically altered. There is some reason to believe that the incidence is increasing in well-fed Western communities, but the expectation of life for diabetic patients—particularly the young—has much increased. Further, the actual causes of death in diabetes have changed. Before the discovery of insulin the commonest cause of death was diabetic coma, but this is now greatly exceeded by cardiovascular disorders. Today vascular disease is the chief problem in the long-term management of diabetes.[1]

It is important to differentiate clearly between the various types of arterial disease. First there is hypertensive arteriolar disease, entirely non-specific, but commoner in diabetic patients than in the rest of the population. Next there is atheroma, affecting only the arteries, and differing only quantitatively from atheroma in non-diabetic subjects. Thirdly—and the most specific—there is the capillary lesion, seen only in the unsupported vessels of the retina and renal glomerulus. Each of these vascular disturbances is quite distinct, having a different pathogenesis, a different course, and different results. Yet they may be found together, so intimately related as to confound all but the most careful inquiries into their separate natures.

Hypertensive changes are usually secondary to renal disease—most commonly pyelonephritis. Urinary infections are so common in diabetic patients that this is no surprise, even in the absence of a history of "pyelitis" or "cystitis" typical lesions are often seen at necropsy. Atheroma, too, may affect one or both renal arteries, and may cause some contributory renal ischæmia, but the resulting arteriolar lesion is in no sense specific, resembling that seen in other types of hypertension.

The incidence of atheroma in diabetic patients is undoubtedly higher than in the general population.[2] Deaths from cardiac disorders and the occurrence of intermittent claudication and gangrene are to be attributed almost entirely to this cause. WARREN and LE COMPTE[3] remark "atherosclerosis emerges without question as the leading cause of death in diabetes, accounting for over two-thirds of all fatalities." Morphologically and chemically the lesion resembles atheroma in non-diabetic patients, and is similarly associated with raised lipoprotein and cholesterol levels in the serum[4], but it tends to affect smaller and more distal vessels[2] and is differently distributed about the body. BELL[5] found that the incidence of occlusive vascular disease of the legs was increased forty-fold in diabetic patients, but coronary thromboses and cerebral vascular accidents, though also common, are not nearly as common as that. There must be some other, unknown, factor concerned with localisation. This is not to imply that the upper limbs are spared. Gangrene of the hands[6] has been recorded, and Dupuytren's contracture is common.[7] LUNDBÆK[8] has described a scleroderma-like condition affecting the hands and associated with calcification in the small blood-vessels, which, he believes, is confined to patients with long-standing diabetes. Cerebral vascular incidents, too, are common. They accounted for 231 cases in a series of 913 diabetic patients admitted with neurological involvement to the New England Deaconess Hospital between 1946 and 1951.[9] The syndrome of headaches and ocular palsies, affecting elderly diabetic patients,[10] may also have a vascular basis—probably atheroma.

The specific diabetic lesion affects only the retinal and glomerular capillaries. First thought to be discrete hæmorrhages deep in the layers of the retina, the red dots seen on retinoscopy have been shown conclusively to represent microaneurysms arising from diseased capillaries.[11] They usually coincide with a characteristic glomerular disorder, which has been described as an "intercapillary glomerular sclerosis".[12] Electron-microscopic studies indicate that the *primary* lesion may be of the basement membrane[13], it is associated with the excretion in the urine of cells containing doubly refractile lipid.[14] The retinal and glomerular capillary lesions are linked by a similarity in the histochemical properties of the hyaline material which accumulates in and around their walls, particularly with special collagen[15] and carbohydrate[16] stains. Moreover, the lesions at each of these sites has been related to certain changes in the sera—notably an increase in complex polysaccharides and glucosamine.[17 18] Possibly the relationship of capillary lesions to these substances is similar to that of atheroma to lipoproteins and cholesterol.

We still know very little of the causes and development of vascular lesions in diabetes. Yet we are not powerless to control them. There is abundant evidence

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[1] *Statist Bull Metrop Life Insur Co* 1957, 38, 1

[2] Semple, R. *Lancet*, 1953 i, 1064

[3] Warren S, Le Compte P M. The Pathology of Diabetes Mellitus, p 130 London 1952.

[4] Baker, R W R., Joiner, C. L, Trounce, J R *Quart J Med* 1955, 24, 295

[5] Bell, E. T *Arch. Path. (Lab Med)* 1950, 49, 469

[6] Lundbæk, K *Ergebn. inn. Med Kinderheilk*, 1957, 8, 1

[7] Wilder, R. M. Clinical Diabetes and Hyperinsulinism, p 299 Philadelphia, 1940

[8] Lundbæk, K. *Acta med scand* 1957, 158, 447

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[10] Jackson, W P U *Brit med J* 1955, ii, 403

[11] Ballantyne, A. J, Lowenstein, A. *Trans ophthal Soc U K* 1943, 63, 95

[12] Kimmelstiel, P, Wilson C. *Amer J Path.* 1936, 12, 83

[13] Irvine, E. Moon H. Unpublished data. Cited by Thompson, R. H. S, King E. J Biochemical Disorders in Human Disease, p 536 London, 1957

[14] Rifkin H Leiter L. Berkman J American Lecture Series in Metabolism Springfield, Ill 1952.

[15] Allen, A. C. *Arch. Path (Lab Med)* 1941, 32, 33

[16] McManus, J F A. Medical Diseases of the Kidney Philadelphia, 1950

[17] Jacobs, H. R. *J Lab clin. Med* 1949, 34, 116.

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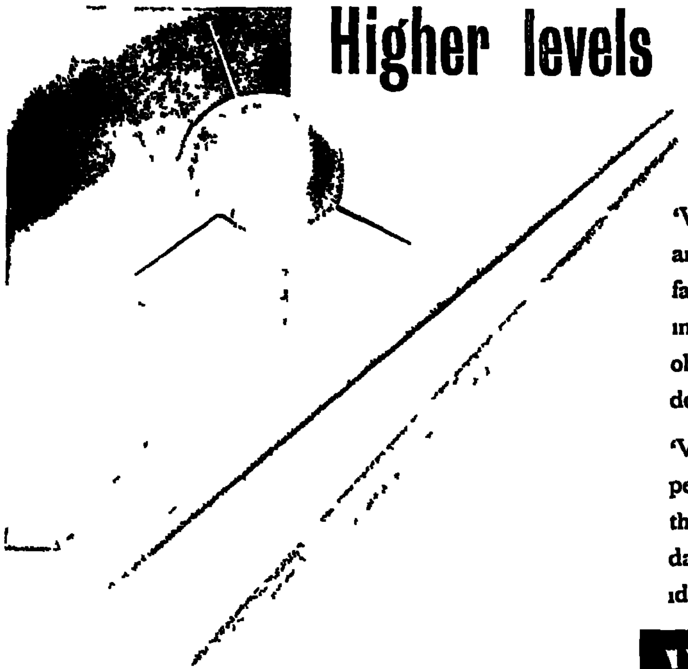

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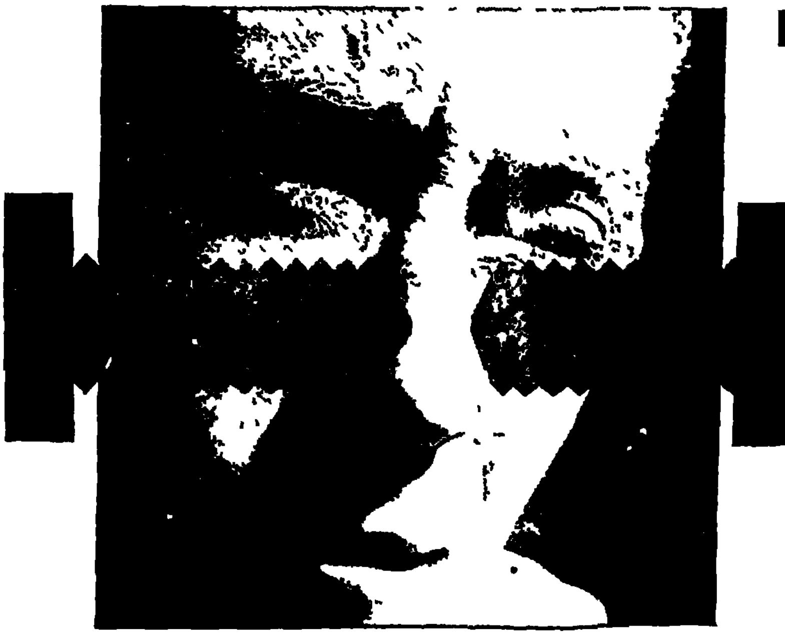

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that the possibility of such complications is greatly reduced by careful control[19]—control as defined by Joslin[20] In addition urinary infections should be treated vigorously, and cryptic pyelonephritis carefully sought Infection upsets diabetic control, and hypertension increases the risks from atheroma and its complications The price of longevity is eternal vigilance

Infectivity of Virus Nucleic Acids

Two years ago we commented[21] on the work of Gierer and Schramm,[22] who had shown that the nucleic acid extracted from tobacco-mosaic virus was infective alone It was to be expected that this work would soon be followed by similar research on viruses of animals and man, and last summer two preliminary reports[23] [24] suggested that infective nucleic acid could be prepared from one of the encephalomyocarditis viruses (Mengo virus) and from Eastern equine-encephalitis virus Now comes a more detailed account by Colter et al[25] of similar investigations with Mengo, West Nile encephalitis, and poliomyelitis viruses

Colter et al homogenised cells infected with these viruses, and then extracted the virus preparations by vigorous shaking with water-saturated phenol The aqueous phase, separated by centrifugation, was designated "ribonucleic-acid solution," and such solutions were found to have an infectivity of about 0 1% of the virus homogenates from which they were prepared The next problem was whether this small residual infectivity was due to a few virus particles which had survived the extraction treatment or to viral nucleic acid First, the "ribonucleic-acid solution" was tested for protein and no detectable protein was found, but this test is not delicate enough to exclude traces of virus Indirect evidence was then sought by comparing the properties of the infective component of the ribonucleic-acid solution with those of intact virus particles Distinct differences were found The infectivity of the ribonucleic acid was inactivated by brief incubation with ribonuclease or simply by long-continued incubation at 37°C, and it was recovered quantitatively after precipitation with molar sodium-chloride solution In these respects the infectivity of the ribonucleic-acid solutions behaved differently from that of intact virus, and there was also a difference in behaviour on high-speed centrifugation Unfortunately, the two types of preparation were not compared after treatment at the same infective titre Nevertheless it seems fair to conclude that the infectivity of the ribonucleic-acid solution is not due to intact virus particles but to viral nucleic acid

The next question was whether the nucleic acid was present in the cells as such and was extracted before being built up into virus particles, or whether it had been extracted from mature virus particles Colter et al answered this question by treating cell homogenates infected with Mengo virus with ribonuclease before carrying out the phenol extraction The ribonuclease treatment had no effect on the amount of ribonucleic acid subsequently extractable from these preparations, and Colter et al conclude that the infective ribonucleic acid was extracted from the Mengo virus particles It should be possible to confirm this conclusion by experiments on purified virus preparations, as has been done with tobacco-mosaic virus Meanwhile, it seems that for a number of small animal viruses the information required to synthesise whole virus particles may reside in the viral nucleic acid alone, and on present theories of nucleic-acid structure this implies that the code for making particles of these viruses is determined by the particular arrangement of their nucleotides on the nucleic-acid chain The protein overcoat of the virus is presumably designed mainly to protect the nucleic acid in an unfriendly world, although from the point of view of the viral host the protein may have other roles But more and more attention is being devoted to understanding nucleic-acid synthesis, with a view to interrupting it where it is becoming inconvenient to man

The Open Door

During the past few years more and more doors have been unlocked in our mental hospitals So far, in setting them ajar, the emphasis has been on egress rather than ingress, but an open door should invite patients to enter as well as to leave The Royal Commission on the Law relating to Mental Illness and Mental Deficiency recognised the importance of easy two-way traffic, and many of their most important recommendations were based on the principle that the patient who is mentally ill or mentally defective should be able to get the shelter and support of hospitals and social services with as little formality as the patient who is physically ill Many of their recommendations will have to await legislation, but it is encouraging that the Minister of Health, in consultation with the Board of Control, is acting without delay on their proposals for changes in the procedure for admitting patients to mental-deficiency hospitals

It is appropriate that a beginning should be made in these hospitals, for hitherto their routine procedures for admission have been more rigid than in hospitals for the mentally ill Only exceptionally have patients been admitted without certification, and the "voluntary" procedure has not been applicable Now they will lead the way, for, thanks to the convenient wording of the present Mental Deficiency Acts, certification is not a legal necessity for these patients, and can, save exceptionally, be allowed to lapse Past official disfavour of informal admission, as the Royal Commission pointed out, was based on "considerations of administrative policy rather than law" The Minister has accordingly recommended mental-deficiency hospitals to admit patients who are willing without certification, and to review their present patients with a view to ending compulsory powers over them where possible.[1] Local authorities have similarly been asked to review patients who are subject to a guardianship order.[2]

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[19] Dunlop, D M *Brit med J* 1954, ii, 383

[20] Joslin, E P, Root, H F, White, P, Marble, A The Treatment of Diabetes Mellitus, p 657 London, 1952

[21] See *Lancet*, 1956, i, 490

[22] Gierer, A, Schramm, G *Nature, Lond* 1956, 177, 702

[23] Colter, J S, Bird, H H, Brown, R A *ibid* 1957, 179, 859

[24] Wecker, E, Schäfer, W *Z Naturforsch* 1957, 12, 415

[25] Colter, J A, Bird, H H, Moyer, A W, Brown, R. A *Virology*, 1957, 4, 522.

The new procedure means that it will no longer be possible to detain these patients in hospital if they want to leave. But in fact the change will, it is hoped, be more apparent in a new climate of opinion than in an exodus of patients. In the present overcrowded state of the mental-deficiency hospitals, medical need must still be the deciding factor in obtaining admission, but patients—and, perhaps even more important, the parents of patients—will accept help more readily and more happily if they feel that they are not at the same time surrendering their rights. Some patients, especially at first, will wish to leave the hospital against advice. In these circumstances the Minister advises that they, and their relatives, should be given the opportunity to discuss the matter fully with the hospital doctor. A patient who persists in his determination to leave should normally be allowed to do so, though exceptionally in his own interests or for the protection of the public he might have to be detained by certification.

One of the most forward-looking parts of the Royal Commission's report was their concern that the mentally ill and the mentally defective should be offered more help and support as part of the community rather than as isolates in hospitals and institutions. Small hostels and welfare services would, the report suggested, make it possible for many of them to share a normal, if sheltered, life with their relatives and friends. The Royal Commission saw the local authorities as the natural administrators of such community services, and undoubtedly these patients offer the public-health doctor a big opportunity in the exercise of preventive medicine and aftercare. This work can only be effective if the mental hospitals and the local authorities draw together. The Nottingham scheme[3] and the Worthing experiment[4] illustrate some of the possibilities, and the new procedures may well provide more. For instance, in his circular the Minister asks that it should become a routine practice for the hospital to notify the local authority when a patient returns to his home. The Minister also points out that the hospital will be even more dependent on the local authority for information about the patient's background and family and for his supervision when he leaves hospital.

Everyone will be glad that it has proved possible to implement so promptly this part of the Royal Commission's report. We trust that the rest need not wait too long on legislation's more deliberate pace.

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[1] H.M. (58)5.

[2] Min. Hlth Circular 2/58.

[3] Macmillan, D. *Lancet*, 1956, ii, 1094.

[4] Carse, J., Panton, N., Watt, A. *ibid.* Jan. 4, 1958, p. 39.

Annotations

HYPERTENSION AND UNILATERAL RENAL DISEASE

HYPERTENSION may be associated with unilateral renal disease, and in many recorded instances a sustained reduction of blood-pressure has followed selective nephrectomy, but it is often difficult to decide on the significance of kidney disease, if present, and, consequently, on the chances of benefit from operative treatment. Experimental evidence, based on the induction of hypertension by partial occlusion of a renal artery and on the demonstration of the renal pressor system, suggests that true "renal" hypertension depends essentially on a vascular lesion. This is supported clinically by the observed occurrence of hypertension in cases of renal ischæmia due either to infarction or to stenosing conditions of the renal artery and its main branches. Research in cases of hypertension of suspected renal origin has, therefore, been directed towards discovering specific vascular lesions which on identification might afford an indication for effective surgical treatment. Poutasse and Dustan[1] have submitted 109 selected hypertensive patients to renal angiography, accomplished by means of translumbar aortography.

They emphasise that aortography should be used not as a routine investigation but only in accordance with certain well-defined indications: firstly, in all cases (regardless of age or the duration of the hypertension) where there is unexplained disparity in the size or function of the kidneys on excretion urography; secondly, in all young patients in whom no other cause can be demonstrated; thirdly, where malignant hypertension develops suddenly in previously somewhat hypertensive elderly patients; and, finally, where there is rapid exacerbation of essential hypertension at any age, particularly if the patient has renal symptoms. Of the 104 patients selected according to these indications, 30 were found to have unilateral or bilateral obstructive lesions of the renal artery, which in many instances were considered to be the primary cause of the hypertension. Most of the lesions were arteriosclerotic plaques causing narrowing of the lumen and associated in some cases with post-stenotic aneurysmal dilatation of the more distal part of the vessel. 19 of these patients were subjected to operation (usually nephrectomy) with gratifying results—the blood-pressure reverting to normal in 5 out of 7 cases followed up for over a year, and in 6 out of 10 observed for shorter periods. Of the 2 patients who died, 1 had been subjected to arterial grafting and the other to attempted endarterectomy.

Discussing the significance of renal arterial disease, Poutasse and Dustan refer both to its potential danger as a cause of hypertension and to the inherent risk of spontaneous rupture of a post-stenotic aneurysm. But in deciding whether to embark on surgical treatment, it should be remembered that only a small proportion of hypertensives have vascular disease restricted to, or predominantly affecting, one kidney, and that local arterial rupture is rare. Unless, therefore, the radiographic evidence is particularly convincing, conservative management with anti-pressor drugs may seem more promising. Nevertheless, Poutasse and Dustan rightly claim that operation is indicated in carefully chosen cases, and they look forward to the time when selection will be aided by detection of renal pressor substances.

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[1] Poutasse, E. F., Dustan, H. P. *J. Amer. med. Ass.* 1957, 163, 1521.

STATISTICS OF SMOKING

THERE is mounting evidence of an association between smoking and malignant and other disease, and there is a real need for dispassionate assessment of the magnitude of this association and the realities of any underlying causal mechanisms The long-term interest of the tobacco manufacturers lies in a free exchange of information between scientific workers concerned with this vital problem, and the publication of a volume of statistics on tobacco consumption[1] by the Tobacco Manufacturers' Standing Committee is a welcome token of their recognition of this viewpoint

Mr G F Todd, statistical adviser to the committee, has produced a most useful volume by collecting from various sources information on the tobacco-consumption habits of different populations both in this country and elsewhere Details are given of time trends in consumption by the type of tobacco used (whether cigars, cigarettes, snuff, or pipes) in different countries From sample surveys done by market-research firms in the United Kingdom, data have accrued on the frequency and type of smoking according to age, sex, job, and place of residence In general, these findings are in line with expectation In truly rural areas, the average daily cigarette consumption of 8 8 per man is less than the 11 3 of the county boroughs, but the lack of information on sampling procedures and size of samples makes it difficult to judge the significance of these differences Some of the other assumptions involved in calculating average consumptions are more explicitly stated in the editorial notes Despite these limitations, the general pattern of the material—e g, on the age-sex trends in smoking habits—is clear enough, and this summary should prove useful in further epidemiological inquiries

SPEEDING THE PATIENTS

YEAR by year the Ministry of Health publishes an analysis,[2] running into 47 columns, of the cost of our hospitals The hospitals are grouped, according to their function and character, under such headings as acute, mainly acute, long-stay, isolation, and mental-illness The analysis aims at providing figures to show the net weekly cost of maintaining a patient To this end the main items of expenditure are divided into two groups—those which tend to vary directly with the number of patients, and those which tend to remain unaltered by the number of beds occupied

Fallacies in the subdivisions have been pointed out in recent years, and these are recognised in the report The main distorting influence is still the assessment of outpatient expenditure This is estimated on the basis that five outpatient attendances cost the same as one inpatient day However in future more accurate information about the real cost of outpatients will be provided, for last April a start was made in the introduction of a full departmental costing system in some 200 hospitals which have an annual expenditure of £150,000 or more The figures which this new procedure will offer when the change-over is completed are awaited with interest

During 1956-57 the weekly cost of maintaining a patient in an acute hospital was £19 11*s*, compared with £17 15*s* in 1955-56 In special hospitals the cost ranged from £8 13*s* in long-stay hospitals to £23 4*s* 6*d* in isolation hospitals These figures had been adjusted (or distorted) to allow for expenditure on outpatients Last year for the first time figures were also given for the cost per patient treated in hospital These provide a telling comparison for hospitals doing the same kind of work, and are perhaps the most important part of the analysis, for they give a clue to where improvements might be made in the hospital service For 1956-57 the average cost per patient treated in "all acute hospitals" was £40 14*s*, compared with £37 12*s* in 1955-56 Generally speaking the cost per patient per week differs only slightly in similar hospitals in the same region, whereas the cost per patient often varies greatly The difference is due not to the percentage bed-occupancy but to the speed of the turnover Many hospitals have found that by careful administration the turnover can be increased without detriment to the patient's welfare, and indeed often to his advantage thanks to earlier ambulation and prompter investigations Scrutiny of the figures suggests that in many hospitals there is still scope for quickening the pace of discharges and admissions

A CANCER FALLACY

THE latest report of the National Cancer Registration Scheme[1] contains much interesting information on treatment and survival, but it also contains some surprising statements about the incidence of the disease They seem to arise from the belief that the liability of an individual to develop cancer at various ages can be deduced from a contemporary set of age-specific incidence or death rates This fallacy is well illustrated in the section on lung cancer In this disease, as is well known, the age-distribution of a large group of patients shows at present a peak in the 7th decade, and the age-specific death-rate is also lower in the 8th decade than the 7th From this the Registrar-General deduces that cancer of the lung is "a disease of middle adult life, the risk of contracting it diminishing in the older age groups", and later that the mortality-rates "justify the conclusion that in England and Wales the risk for women of contracting lung cancer does not increase after the age of 70 but much more probably falls, while after the age of 65 the risk for men certainly falls"

These statements are not supported by the available evidence It is true that the death-rate of people over 70 who die of lung cancer is smaller than the death-rate of those aged 60 to 69, and the risk of death from this cause is greater at present for an individual aged 65 than for one aged 75 But it cannot be inferred from this that the risk for the older individual was greater ten years ago or that the risk for the younger will be less in ten years' time The changing incidence with advancing age can be studied only by following the experience of a group of individuals through their successive ages In practice, this is done by the method of cohort analysis Using this technique Korteweg[2] in 1951 and Case[3] in 1956 showed that the risk of death from lung cancer increases throughout life There is, in fact, no falling off after middle life Thus, the death-rate among those now 75 is higher than it was ten years ago among the group then aged 65, of whom they are the survivors Those aged 65 at present are suffering a higher rate than were people of the same age ten years ago.

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[1] Tobacco Manufacturers Standing Committee Research Papers no 1 Statistics of Smoking, edited by G F Todd Published by the committee, 6 Bruton Street London, W 1

[2] National Health Service Hospital Costing Returns, March 31, 1957 H M Stationery Office £1 2*s* 6*d*

[1] Supplement on Cancer Registrar General s Statistical Review of England and Wales for the Year 1952 H M Stationery Office, 1957

[2] Korteweg, R *Brit J Cancer*, 1951, 5 21

[3] Case, R A M *Brit J prev soc Med* 1956, 10, 172

The "fall" of death-rate from lung cancer in old age is, therefore, an expression not of diminished individual risk in old people but of increased risk in the younger ones. The current death-rate among an age-group is the latest term in a series of rates stretching back year by year to the birth of all individuals in the group, and the rates may vary with, among other things, the changing environment. The individuals taking part in a contemporary age-specific rate are not the same as those in any other contemporary rate, nor can they have been subjected to exactly the same environment. In the case of lung cancer some of the relevant factors in the environment are known to have changed considerably, for the practice of cigarette-smoking increased rapidly in the early part of the century. Thus, those now 65 have been more exposed to this hazard than were those who were 65 ten years ago, and the impact of the disease on them is correspondingly greater. The application of the method of cohort analysis to cancer mortality was clearly described recently by Case,[4] who emphasised its great value as a historical or narrative technique for displaying the changing patterns of mortality.

OPERATING-THEATRES

PERHAPS the most significant change in operating-room mechanics in the past twenty years has been, in a sense, a return to Listerism. Antisepsis inculcated an aggressive approach to organisms, which were attacked even in the air; this attitude changed with the advent of asepsis to one rather of peaceful coexistence, and conveniently the hazard of airborne organisms in theatres was almost forgotten, for how could air be sterilised? Yet some remained vigilant. Hart[5] showed that hæmolytic *Staphylococcus aureus* was the predominant organism in 90% of unexplained wound infections, that this organism was not to be found in recently laundered materials, that the staphylococcus obtained from the skin and sweat of staff and patients was usually *Staph. albus*, almost never hæmolytic *Staph. aureus*, and that *Staph. aureus* could invariably be obtained from the air of the operating-room. Air contamination was worse in winter, and the source appeared to be the nasopharynges of those working in the theatre. After introduction of air sterilisation by ultraviolet irradiation, wound infection fell to a hundredth of its previous level in thoracoplasties and mastectomies. In this country Cairns[6] was concerned about airborne infection of neurosurgical cases from similar sources. But the source contaminating the air pool does not always lie within the noses of those working in the theatre. Sevitt[7] found that two cases of tetanus were due to introduction into the theatre of spores from plaster hair being used for building repairs nearby; he indicted the ventilation system, and yet had the discouraging experience four years later of having to report gas-gangrene infection due to the still faulty system.[8]

Except for a few hospitals equipped with the plenum heating system, the standard ventilation system during half a century of asepsis has been on the exhaust principle in order to get rid of steam from the sterilisers and to provide comfortable working conditions for surgeon and staff; air is changed by extraction. The possibility that organisms from outside the theatre might thus be sucked in was long ignored, and so the great majority of our hospitals today, even those built just before the late war, have to face a new era of infection with dangerous equipment. A bulletin just published by the Ministry of Health,[9] the first of a series to help those concerned with designing and planning hospitals, is particularly welcome since it recognises the *volte-face*—the return to the attack on airborne organisms. Both ultraviolet radiation and aerosols are dismissed as means of air sterilisation. Instead it is recommended that positive-pressure systems of ventilation be installed in all new theatres so that organisms shed within the theatre are blown out, while dust and organisms outside are driven away from its precincts. But installing a positive-pressure system cannot alone ensure security,[10] since the current of air may disturb dust lying on the floor; its direction must be controlled in the light of smoke tests. Moreover vertical shafts connecting suites of theatres tend to develop into extraction systems owing to a Venturi effect as warm air rises up them, thus nullifying the attempt at positive pressure—yet another reason for constructing theatre suites in horizontal, as the bulletin recommends. There is one quite important omission. Sometimes people outside the theatre—usually members of the medical staff—need to speak to the surgeon while he is operating. This is best done by means of microphone and speaker circuits, which obviate disturbance due to movement in and out of the theatre—movement which Bourdillon et al.[11] have shown to be followed by an increase in airborne organisms.

One innovation in the layout of the theatre suite is the inclusion of a recovery room—an admirable recommendation which may nevertheless evoke controversy. All would agree on the need for a site to be set aside where the anæsthetist may readily reach the patient who has just been operated on, while still conducting the rest of the operating-list; a third of all anæsthetic deaths occur within half an hour of the end of the operation, and these are almost invariably due to obstruction of the airway. But some would remove the recovery room from the theatre and place it, as a recovery ward, immediately adjacent[12]; they insist on the need for such a ward not only for immediate postanæsthetic care but for the first two or three days after operation when the patient can (it is claimed) be better treated in this special ward and the staffing of the ward he has come from can be correspondingly lightened. Recovery wards are the vogue in the New World, where they doubtless help to reduce the handicap of the scarcity (even greater there than here) of experienced nurses. Where this scarcity is not so great, the other practical advantages of concentrating postoperative patients in a single ward must be set against the disadvantage of requiring them to enter a new environment at a time of special stress. Any patient coming into hospital is quite suddenly alone, with human contacts—those stabilising factors in life—severed. Accordingly he must set about establishing new contacts, with the staff and his fellow patients. To the surgical patient the new contacts that he establishes before operation are especially valuable in the first few postoperative days.

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[4] Case, R. A. M. *Brit. J. prev. soc. Med.* 1956, 10, 159.

[5] Hart, D. *J. Amer. med. Ass.* 1941, 117, 1610.

[6] Cairns, H. *Lancet*, 1939, i, 1196.

[7] Sevitt, S. *ibid.* 1949, i, 1075.

[8] *ibid.* 1953, ii, 1121.

[9] Hospital Building Bulletin no. 1. Operating Theatre Suites. H.M. Stationery Office. Pp. 76. 9s.

[10] Paterson Ross, J. *Brit. med. J.* 1956, i, 702.

[11] Bourdillon, R. B., McFarlane, A. M., Thomas, J. C. *Spec. Rep. Ser. Med. Res. Coun., Lond.* 1948, no. 262, p. 241.

[12] See *Lancet*, Jan. 11, 1958, p. 91.

Public Health

PROBLEM FAMILIES

A London Survey

J A Scott
O B E, M D Lpool, F R C P, Q H P
MEDICAL OFFICER OF HEALTH FOR THE COUNTY OF LONDON

The Minister of Health in 1954 encouraged local health authorities to develop their work in preventing the break-up of families, and in particular to see what they could do to break the vicious circle in which problem families tend to reproduce themselves in the next generation—at an expense to the community out of all proportion to their numbers He suggested that this work might be done through the redeployment of existing health visitors rather than by an increase in their number, but the employment of a trained social worker might be useful

Our first task in London was to ascertain how many families needed help on the lines suggested, and to estimate how many needed intensive care which could be undertaken only by a case-worker with a small case-load or by a combination of social case-workers With my colleagues in the education and welfare departments a survey was made covering all families with a child or children under the age of 15 My department investigated the families in which there was a child under 5 living at home, the education department investigated those in which all the children were older, and the welfare department dealt with families in homeless-family units or halfway houses So far as numbers are concerned, therefore, the data given are complete, but the detail relates only to the families with which my department was primarily concerned

Planning

Families may be classified broadly into five groups

1 Above normal visiting standard
2 Socially sound
3 Families with difficulties
4 Potential problem families
5 Hard-core problem families

The survey was concerned with the selection of these two last groups

Potential problem families may be defined as "those in which there are early signs of failure which may lead to disruption of normal home life with consequent risk to the children", and hard-core problem families as "those which are unable, by their own efforts to raise themselves from the state into which they have fallen or to take advantage of the social services of which they are in need" There are, however, many other definitions, and it was felt that any inquiry based solely on qualitative criteria would lead to subjective assessments by health visitors and others, from which no valid conclusions could be drawn Accordingly the factors which were likely to be found in such families were listed and points allocated to each factor this provisional pointing system was tested by application to the circumstances of a number of families and modified in the light of the tests The factors and points awarded them were chosen arbitrarily, but they provide a clear and uniform basis for a survey, moreover they enable comparable assessments to be made in later years A maximum of five discretionary points was allowed for imponderables

The list of factors and the points awarded are set out below, for brevity certain detail has been omitted, such as guidance on the interpretation of the terms drinking, gambling, and promiscuity as factors, and the period over which they should have been operative

FACTORS LIKELY TO BE FOUND IN PROBLEM FAMILIES

1 *In a parent*
  (a) Low intelligence or mental deficiency
  (b) Mental illness
  (c) Physical handicap or illness which prevents work or permits of light work only—e g, tuberculosis, heart-disease
  (d) Long-continued or recurrent unemployment of main wage earner from other causes than physical handicap or illness
  (e) Excessive drinking
  (f) Excessive gambling
  (g) Sexual promiscuity
  (h) Serving, or has served, a prison sentence
  (i) Suspected cruelty to or neglect of children
  (j) Known cruelty to or neglect of children

2 *Other parental shortcomings*
  (a) Persistent quarrelling
  (b) Failure to call doctor for major illness
  (c) Leaving young children unattended

3 *In a child*
  (a) Repeated hospitalisation of one or more children for gastroenteritis or respiratory disease, or two or more children for minor accidents
  (b) Persistent truancy
  (c) Juvenile delinquency (court cases only)
  (d) Attendance at child guidance clinic
  (e) Under Probation Officer or committed to care by a court

4 *Housing*
  (a) Statutory overcrowding
  (b) Living in intolerable conditions (while not overcrowded) because of either lack of amenities such as piped water, damp or insanitary conditions, and/or enmity of other occupants of dwelling

5 *Poverty and mismanagement*
  (a) Chronic family debt
  (b) Lack of minimal necessities of furniture and bedding
  (c) Inadequate and irregular meals
  (d) Domestic filth and disorder
  (e) Wilful damage to property
  (f) Lack of, or inadequately maintained, clothing of children

6 *General*
  (a) Unnecessary crowding at night
  (b) Gross personal uncleanliness
  (c) Failure to take advantage of necessary help and service proffered.
  (d) Child or children taken into care other than as the result of court action, and who are frequently taken into or out of care

Allocation of Points to Factors

1 1 point was allotted for the existence, whether one or more persons was affected, of each factor in the list, except in section 1, where for items (*a*) to (*i*) the pointing was

For one parent—1 point
For both parents or the sole parent—3 points

and for item (*j*) the pointing was

For one parent—$1^1/_2$ points
For both parents or the sole parent—4 points

2 Additional points or fractions of points, up to a maximum of 5, could be added by the reviewing officer to deal with imponderable factors not listed—e g, persistent sickness of children, mental or physical cruelty of one parent to another, racial differences between parents, spasmodic reappearances of deserted, divorced or separated parent (which upsets stability), a combination of items which do not of themselves merit points, such as domestic disorder (without filth), poverty with spasmodic debt, large numbers of children under 5, and inadequate (but not irregular) meals

3 The maximum pointing was 56, and for the purposes of classifying the families assessed the following arbitrary values were used

Hard-core problem family—11 points or more
Potential problem family—5–10 points inclusive

The differing social conditions in various parts of the county, and the lack of any real knowledge of the numbers and location of problem families, made it necessary to have a complete survey rather than a sample

Operation

The county comprises nine divisions, each administered by a divisional medical officer In each the health visitors were asked to make a provisional selection of potential and hard-core families from their total case-load (in London a case-paper is made out for every child born to a resident and is kept in a family folder at the local clinic) Family case-histories, selected by the health visitors and supplemented by discussion, were considered by the divisional nursing officers in each division (who were appointed reviewing officers) to assess the factors and to grade the families Health visitors made a note of the time actually spent for a period of four weeks on the families finally selected Finally a central team (Principal Medical Officer (Maternity and Child Welfare), Statistician, and Chief Nursing Officer) visited a number of centres in the divisions and interviewed the health visitors Ten centres were visited and 39 health visitors were interviewed The centres were chosen to represent a cross-section of the London population as regards social class

The relationship of health visitors with other field workers of both voluntary and statutory bodies called in to assist the family, the attitude of the family towards advice and help, and the limitations imposed by their willingness or ability to accept advice, were all taken into consideration in forming an estimate of the amount of time which should be spent on these families

Numbers

Families with a Child under 5

Table I sets out the number of families surveyed by the public health department The figures shown tend to be an underestimate, because constant immigration means that at any given moment there will be new families in the county whose circumstances are not fully, if at all, known, moreover, with the turnover of health visitors, there were some who, at the time of the assessment, could judge only from case papers, which, however well kept, are no real substitute for personal knowledge of the family

The difference between the average and maximum numbers of problem families in the care of a full-time health visitor confirmed the impression that problem families tend to be grouped in small areas

Also they tend to move about for example, of 30 families in the case-load of one health visitor, 6 had moved out of her district in three months They may also move in and out of the various categories as their circumstances change for example, in one division there were at the time of the survey 314 problem families in all, whereas six months later the total had fallen to 303 The net fall of 11 families was made up of a much larger fall in the number of potential problem families offset by a rise in the number of hard-core problem families

TABLE I—NUMBERS AND PERCENTAGES OF PROBLEM FAMILIES IN FAMILIES WITH CHILD UNDER 5

No of families surveyed	with children under 5 only	103,172
	with schoolchildren also	68,699
	total	171,871
No of potential problem families	among those with children under 5 only	569
	among those with schoolchildren also	1225
	total	1794
No of hard-core problem families	among those with children under 5 only	146
	among those with schoolchildren also	516
	total	662
Percentage of potential problem families of	those with children under 5 only	0 55
	those with schoolchildren also	1 78
	all families surveyed	1 04
Percentage of hard-core problem families of	those with children under 5 only	0 14
	those with schoolchildren also	0 75
	all families surveyed	0 39
Percentage of problem families of	those with children under 5 only	0 69
	those with schoolchildren also	2 53
	all families surveyed	1·43
Average no of problem families in the care of a full time health visitor	potential problem families	4
	hard-core problem families	2
	all problem families	6
Maximum no of problem families in the care of a full time health visitor	potential problem families	27
	hard-core problem families	18
	all problem families	33

The 171,871 families surveyed which have a child or children under 5 comprises, as far as can be estimated, virtually the total that exists

Our belief that in this respect the survey was almost complete is supported by the results of an earlier investigation in which the number of children under 5 with whom the health visitors were in contact was compared with the Registrar General's population estimate, and with a current estimate of the number of families of differing compositions, taking into account migration and birth and death rates The number of problem families ascertained is unlikely to be too few, since these families are characterised by their demands, voluntary and involuntary, on the social services

The rates for the two categories of problem family combined ranged from 0 52% in division 7 (Camberwell and Lewisham) to 2 28% in division 5 (Bethnal Green, City, Poplar, and Stepney) the county average was 1 43% The estimated percentage of problem families, based on an investigation of 1000 families in Newcastle upon Tyne, was 2, but, as the authors of the report[1] make clear, " the difficulties of measurement and the way the families were selected should be borne in mind " In a large urban county such as London, which contains within its boundaries such widely differing types of locality, larger interdivisional differences might have been expected, but in fact the percentage incidence of problem families in the remaining seven divisions ranges from 1 04 to 1 80

The lowest figure merited further investigation Possibly it was attributable to the stable staffing in the division concerned, moreover, for a long period the senior nurses had given positive direction to the work with these families, and home helps had been used to assist in more intensive efforts in the homes

As might be expected, there were fewer hard-core problem families than potential problem families—662 as opposed to 1794, and in both the potential and hard-core groups there were fewer families among those with children under 5 only than families with children under and over 5—in total 715 as opposed to 1741—although there were only 69,000 mixed families compared with the 103,000 families with children under 5 (Despite fluctuations in numbers these findings are consistent among all divisions) Among families with a child or children under 5 years of age the percentage incidence of potential and hard-core problem families was 0 55 and 0 14 respectively, among families with children both under and over school age the corresponding percentages were 1 78 for potential and 0 75 for hard-core problem families It is assumed that the reason for the higher percentages of problem families among the " mixed " ones is that they are probably larger and/or poorer so that the mother cannot cope—there seems to be a limit to the difficulties with which a stable but dull parent can compete, after which one further adversity will produce a complete breakdown in domestic management

Families with no Children under 5

Among the families cared for through the education care-committee organisation were 427 potential problem families and 99 hard-core problem families

It is proper to note that an attempt had to be made by the care-committee organisers to award points for the various factors as revealed by the case-histories in the office files, and, whereas the families where children had been reported to the

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[1] Spence J, Walton W S, Miller, F J W, Court, S D H A Thousand Families in Newcastle upon Tyne London 1954

TABLE II—TOTAL NUMBERS OF POTENTIAL AND HARD-CORE PROBLEM FAMILIES

Problem family	Children under 5 only	Children under and over 5	Children all over 5	In welfare homes	Total
Potential	569	1225	427	18	2239
Hard-core	146	516	99	22	783
Total	715	1741	526	40	3022

National Society for the Prevention of Cruelty to Children (N S P C C) or the Education Officer's Problem Case Conferences were reasonably well documented, full data were not usually available in other cases The assessment of families into the two categories was therefore somewhat subjective

The percentages, based on an estimated number of families, were 0 21 for potential and 0 05 for hard-core problem families The rate for both (0 26) is about two-fifths of that for families with children under 5 years only and a tenth of that for families with children over 5 also

As the families reported on by the care organisers were not increasing and the children were all benefiting from the school and school-health services it might have been expected that the percentage would be below that for the mixed families The numbers reported may, because of the reliance mainly on case papers, be an understatement—i e , in some households in which the children are all of school age—the mothers' responsibilities are lessened and the more obvious evidence of neglect may tend to disappear, but other manifestations, such as truancy or juvenile delinquency are apt to take their place, while such factors as low intelligence or housing difficulties remain

Families in Homeless Family Units and Short-stay Accommodation

Within this select group of families, the wardens of the homeless family units chose those which appeared to come within the definition of potential and hard-core problem families There were, in a total of 645 homeless families, 18 thought to be potential and 22 hard-core problem families In terms of percentages, therefore, potential problem families amounted to 2 8 of the total, hard-core families to 3 4, and the two together 6 2 These figures are obviously not comparable with those obtained by more exact standards, but the incidence of problem families so selected was slightly more than four times as high as that ascertained in the public-health department of families living in their own home

TABLE III—PERCENTAGE INCIDENCE OF FACTORS AMONG ABOUT 1000 PROBLEM FAMILIES WITH A CHILD OR CHILDREN UNDER 5

Factor	Potential problem families	Hard-core problem families	All problem families
Parent			
Low intelligence	42 2	67 3	50 9
Mental illness	16 5	13 8	15 6
Illness or handicap	18 2	18 1	18 1
Unemployment	26 5	46 7	33 5
Excessive drinking	13 8	25 5	17 8
Excessive gambling	8 3	14 3	10 4
Sexual promiscuity	19 1	32 1	23 6
Prison sentence	12 8	22 6	16 3
Suspected cruelty (or neglect) to children	21 1	31 2	24 6
Known cruelty (or neglect) to children	15 9	45 8	26 3
Parental shortcomings			
Quarrelling	40·5	51 9	44 5
Failure to call doctor	2 8	12 0	6 0
Leaving children alone	13 8	37 0	21 8
Child			
Repeated admission to hospital	18 8	26 1	21 3
Persistent truancy	4 3	10 3	6·4
Juvenile delinquency	20 5	11 2	7 3
Attendance at child-guidance clinic	4 3	5 2	4 6
Under probation officer, &c	8 7	15 8	11 2
Housing			
Overcrowding	28 4	35 5	30 9
Intolerable conditions	31 5	44 1	35 9
Mismanagement			
Chronic debt	24 6	51 9	34 1
Lack of furniture	25 4	54 2	35 4
Inadequate meals	38 2	70 5	49 5
Filth and disorder	32 1	59 3	41 6
Wilful damage	5 2	20 1	10·4
Children inadequately clothed	27 4	60 7	39·0
General			
Unnecessary crowding	9 6	20 6	13 5
Uncleanliness	16 5	41 5	25 2
Help refused or abused	30·4	51·0	37 6
Children taken into care	11·0	21 5	14 7
Imponderable factors	76 1	59 3	70 3

Total Numbers

From all departments, there was reported a total of 3022 families, 2456 from those with a child or children under school age, 526 from those with children of school age only and 40 in welfare establishments (table II)

In five recent surveys in other parts of the country,[2] the figures of incidence range from 1 2 to 6 2 problem families per 1000 total families The bases of the various inquiries were not uniform, and the figures should be treated with some reserve There are in London some 1,100,000 families, but only about 400,000 of them have a child or children under 16 The London total works out at about 2 75 problem families per 1000 total families, though, as will be apparent from what has been already said, the various components of the total number were not all arrived at in quite the same way, and more reliance can therefore be placed on some than on others

Ætiological Factors

After the survey was well advanced it was decided to analyse the ætiological factors in problem families in four divisions The number of problem families reviewed was about 1000 and the factors assessed are shown in table III

There were, as might be expected, a number of differences between the divisions in the incidence of such factors as long unemployment or lack of amenities The table again separates the families into the potential and hard-core categories a further subdivision was made into those with all children under five years of age and the mixed families, but this has been omitted from the table, largely because nothing of importance was revealed

The salient features are, first, the high amount of emotional instability—if it be accepted that excessive drinking, excessive gambling, sexual promiscuity, and persistent quarrelling are symptomatic of instability 54 5% of potential problem families and 71 6% of hard-core problem families reveal emotional instability by one such symptom The second feature is the high incidence of low intelligence or mental deficiency 42 2% of the potential problem families and 67 3% of the hard-core (It is admitted that low intelligence has not been defined and is therefore a matter of judgment of the individual health visitor)

It is a matter for conjecture whether anything substantial can be done through the normal health services for the families in which emotional instability is combined with low intelligence This group accounts for 19 1% of the potential problem families and 45 8% of the hard-core, but instability, as evidenced by the four symptoms chosen, is in fact combined with normal intelligence or above in no less than 35 4% of the potential problem families and 25 8% of the hard-core

The third feature is the proportion of families in which there was known or suspected cruelty or neglect Allowing for overlapping, in that some families had both, say, known neglect and suspected cruelty, the percentages were 34 6 in the potential problem families and 77 1 in the hard-core Within this group there are families in which neglect may amount to cruelty, yet the family remains an entity because there is affection between parents and

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[2] Blacker, C P Problem Families Five Inquiries London, 1952

TABLE IV—TIME SPENT BY HEALTH VISITORS ON PROBLEM FAMILIES WITH A CHILD OR CHILDREN UNDER 5

—	Minutes per week per family			Total hours per week
	Average	Maximum	Minimum	
Potential problem families	20	270	0	606
Hard-core problem families	28	210	0	308

children This is not, of course, a matter which affects local authorities alone—many of the families being under the scrutiny of the N S P C C or the probation service Nevertheless the figures are profoundly disturbing

The fourth feature is the environment housing, there were overcrowding or intolerable conditions (including enmity of neighbours), or both, in 44 3% of potential problem families and 60 2% of the hard-core, allowing for overlapping Whether bad housing dragged the family down, or whether the unsatisfactory family inevitably gravitated to bad conditions is a matter which can be decided only after careful sifting of the individual family circumstances

Finally, 30 4% of the potential problem families and not less than 51% of the hard-core failed to take advantage of the help and services proffered

Time Spent by Health Visitors

Table IV shows the average time spent per problem family per week by health visitors, together with maxima and minima

The county averages were twenty minutes a week for a potential problem family and twenty-eight minutes for a hard-core one In every division of the county more time was spent on the hard-core than on the potential problem families The maximum times are almost without exception the result of a crisis in one or more of the families concerned—such as a mother temporarily deserting her children, an economic crisis, infidelity, a child being in trouble for truancy, assault or theft, or illness in a parent—which has caused the health visitor to devote perhaps the whole of her time for several days to solving the particular issue

It may seem surprising that the minimum times are nil, but this is due to such causes as the absence of the family (hop-picking), the temporary stability of the family, or the occasional unwillingness to accept the health visitor The fact that a visit would be unwelcome does not mean that the family is neglected Quite apart from information garnered from other social workers, health visitors learn a great deal about their families as they go about their district which is not reflected in the times recorded they may meet the mother in the street or the children at school, they see friends, neighbours, and relations, and some mothers will seek out the visitor at the centre when they are in trouble Another reason for low times spent is that, as was shown in table I, a few health visitors had to deal with a concentration of problem families—a concentration too great in some cases for them to carry adequately The information revealed by the survey has led to a certain amount of " load spreading " It is impossible wholly to equalise this particular burden because of the location of the families and the demand of other duties undertaken by health visitors Again health visitors do not work in isolation almost always there were two or more social workers dealing with a problem family, and if they are working together responsibility is shared and visits by either one become less frequent

A decision of the average amount of time that could usefully be spent on families in the two categories was a matter of some complexity There were variations in family customs, outlook, size, age, structure, housing, and so on, as well as constantly changing family circumstances In some cases Family Service Units are actively engaged in work with problem families as well as the Family Welfare Association, N S P C C, Area Children's Officers, &c a service of specially trained home helps has recently been introduced to work with the health visitors Moreover, the practice has been developed of health visitors working in teams, which has led to a pooling of ideas, abilities, and experience (not least in the linguistic and religious fields), and has enabled families to be transferred from one health visitor, with whom they may no longer be en rapport, to a colleague on the team this teamwork has provided for an easier transference of care in times of staff sickness and a means of overcoming the feeling of staleness that overtakes at times even the most enthusiastic of workers In addition, where the father was the stable element in the household, the health visitor has made contact with him in the evenings or at weekends the need for a male worker has been apparent in cases where the father has been recalcitrant or sexual problems have been involved, and, in these circumstances, health visitors have sought the aid of male workers of the N S P C C or National Assistance Board The general practitioner can be immensely helpful when an authoritative approach to the father is required

There is a wide range of times about the averages (table IV), and the maximum times are themselves averages of time spent on the families in the care of an individual health visitor, in short it seems that when a family was known to be going through a period of crisis, additional time was given by the health visitor, though possibly at the expense of other duties

It is clear that more time could usefully be spent on both categories of problem family than the averages of twenty and twenty-eight minutes a week Extra time is required to rehabilitate some families where intensive help is needed But the number of health visitors is unlikely to increase much in the near future If such selected families could be passed to social case-workers, who might *on average* give up to ninety minutes a week to them, some progress might be made The health visitors would, of course, continue to visit on health aspects, but would be relieved of the intensive case-work on these selected families The time thus saved by the health visitors could be devoted to the balance of problem families for which they are responsible

Summary and Conclusions

The prevalence of potential and hard-core problem families has been surveyed in the nine divisions of the county of London The total number of such families ascertained was 3022 Of these 2456 had a child or children under 5 526 had children above that age, and 40 were in welfare establishments

The following figures refer to families with a child under 5

1 The percentage prevalence in the divisions for both ranged from 0 52 to 2 25, with a county average of 1 43 (if these extremes are ignored the range was from 1 04 to 1 8)

2 An analysis of ætiological factors in 1000 families revealed emotional instability in 54 5% of the potential and 71 6% of the hard-core problem families, low intelligence or mental deficiency in 42 2 and 67 3% respectively, known or suspected cruelty or neglect in 34 6 and 77 1%, overcrowding or intolerable housing conditions in 44 3 and 60 2%, failure to take advantage of help and services proffered in 30 4 and 51 0%

3 The average amount of time spent weekly by a health visitor in London was twenty minutes per potential problem family and twenty-eight minutes per hard-core problem family

4 If social workers could be employed for time-consuming case work on selected families, an additional effort could be made to rehabilitate these families, and the health visitors would be relieved to that extent of their responsibilities, although continuing to visit on health aspects The time saved by the health visitors could be devoted to the remaining problem families

To test the advantages of using social workers in this way, they have now been given the main responsibility for the support of a number of selected families

Many hundreds of my colleagues—doctors, nurses, administrators, and statisticians—have taken part in this investigation I am indebted to them all, and in particular to Dr M MacGregor, Dr D Egan, Mr G Berridge, Mr C W Shaddick, and Miss E Robinson

LONDON'S HEALTH IN 1956

There was no startling change in the health of London between 1955 and 1956 [1] Dr J A Scott, the county medical officer of health, records that in 1956 the infant and maternal mortality rates reached new low records, the death-rate and notification-rate for tuberculosis continued to fall (for the first time on record no male under 25 died from pulmonary tuberculosis), but notifications of dysentery were the most numerous on record The illegitimate live-birth rate (8 5 per 100 live births) was by far the highest since the war-years' average of 8 4%, and the suicide-rate rose from 0 14 to 0 15 per 1000 (since 1920 it has varied from 0 11 to 0 15)

Public-health work is today extending its scope to encompass attempts to prevent mental illness, respiratory disease (through attacking air-pollution), and home accidents, all of which are common causes of death and disability The three appendices to the report are thus of special interest

The first concerns "problem families"—i e, those who have not responded to the general improvement in social conditions and cannot by themselves improve their position or make use of social services Children of such families are prone to physical neglect and mental disturbance The appendix sets out the services dealing with problem families and reports a survey (described by Dr Scott in an article on p 204 this week) made to discover the number of potential and hard-core problem families—together these comprised 1 43% of the families in the county, with figures ranging from 0 5% in one division to 2 2% in another

The second appendix describes investigations that sought to discover links between atmospheric pollution and mortality from respiratory disease At 7 recording-stations, the smoke and sulphur-dioxide content of the air were measured in the winters and summers of two years, the measurements and some other factors (social class, percentage of residents born in London) were compared with the death-rates from respiratory and other diseases Dr Scott sums up the results thus

> "The bare fact of long residence in London appears to be likely to increase the risk of dying particularly from bronchitis, the effect of a smoky atmosphere is also to increase the risk but while a brief sniff of sulphur dioxide is not particularly harmful the dual effects of both high pollution and long residence in London are associated with high mortality Association is, however, not necessarily a matter of cause and effect The reason for the poor numerical association of mortality with the indices of atmospheric pollution in [various areas of] London may be that the differences within London are not sufficiently large to demonstrate any difference"

During fog, acute "smog incidents" with many deaths were likely when the pollution of the air reached a threshold of four times the normal winter level

In his third appendix Dr Scott points out that the total number of deaths from home accidents rose by about 25% between 1950 and 1955 The small decline in deaths from suffocation and in deaths of young children was more than offset by the increase in deaths from falls, poisoning, and burns, and in deaths in old people The causes of accidents are broadly inexperience in the young, inattention in the adult, and infirmity in the elderly Safety devices, such as fireguards, even when properly used are only a partial and temporary substitute for constant supervision of children The appendix sets out methods of instruction in home safety, including exhibitions, school, newspaper, and cinema publicity, and the training of home nurses and health visitors

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[1] London County Council Report of the County Medical Officer for the year 1956 Pp 244 2*s* 6*d* Obtainable from the Council, County Hall S E 1

The Wider World

SCHISTOSOMIASIS IN CHINA

BRIAN MAEGRAITH
M A, D Phil Oxon, M B Adelaide, F R C P, F R C P E
PROFESSOR OF TROPICAL MEDICINE, SCHOOL OF TROPICAL MEDICINE, LIVERPOOL

SCHISTOSOMIASIS* is regarded as the most serious parasitic disease in China Its extent is not yet fully known, but in the area of the Yangtse valley and the rich lands to the south recent surveys have revealed over 11 million persons infected, and local infection-rates ranging from 10% to 70%

The physical consequences of schistosomiasis in the individual sufferer are often savage, as will be seen below, but the effects on the community as a whole are even more disastrous, since it has been estimated that the disease, which is manifest particularly in young adults and in middle age, reduces the working capacity of those affected to well below half normal

In a predominantly farming community the economic significance of this incapacity is immense As the population grows increasing pressure is brought to bear on the farmers to produce more food To do this they must be able to work at their top capacity, which demands good health It is not surprising, therefore, that China is turning all her available resources to checking clinical schistosomiasis, and controlling its transmission

A nation-wide scheme of control has been evolved within the last two years and is now in operation and expanding rapidly The two main points of attack are (1) the mass treatment of overt infections with the object of bringing clinical relief and reducing the output of infective *Schistosoma japonicum* eggs in the fæces, and (2) the control and eventual elimination of transmission by preventing the pollution of water by human and animal fæces containing ova and by destroying miracidia and cercariæ and the amphibious intermediate snail host oncomelania

The development and progress of the scheme is the political responsibility of the Ministry of Health in Peking, which works through a small executive lay committee and associated technical groups in Shanghai In the twelve provinces concerned antischistosomal centres with trained staff have been established for purposes of mass treatment, propaganda, and training of local recruits and for the general administration of regional control Subsidiary units have been created in the smaller districts right down to the villages and cooperative farms The actual field work at this level is done by the local farming or village communities, who have among themselves organised trained teams for controlling transmission within their own territories In this way the local community is acting for itself in its own interests and cooperating at the same time in the wider national scheme

The Chinese Government quite rightly regards propaganda as an essential technique in the antischistosomal scheme and has organised public information services in the endemic areas on an impressive scale, with the twofold object of achieving control of the disease and of obtaining a more general improvement in social health and cleanliness and, even more important, a genuine desire for an improving standard of living Working through radio, village communal news-sheets, talks, cinemas, and village committees (often containing a member of the Communist Party), the propaganda is persistent and all-pervading and is clearly getting results, some of which, such as the astonishing control of flies and litter, are immediately obvious to the visitor

In effect, " this nation-wide campaign, unparalleled elsewhere in the world, has brought about great improvement in personal hygiene and environmental sanitation and is instrumental in helping to eliminate conditions under which diseases like schistosomiasis are disseminated " (*Chinese Medical Journal*, 1955)

The cooperative effort demanded in such a campaign is not limited to the relations between the people and the health authorities only Active help and advice are needed in addition from allied services, including agriculture, forestry, and water conservancy, for carrying out vital operations such as draining, ditching and reclamation of low-lying land, especially in potential flood areas The remarkable degree of integrated cooperation already achieved, perhaps more easily in China than in non-totalitarian countries, augurs well for the future success of the whole scheme

The Chinese have set as their target the practical control of schistosomiasis within twelve years from now Their cooperative enthusiasm, skill, and dedication to the task should enable them to achieve this objective

During a recent visit to China with a group of doctors from the United Kingdom I was fortunate enough to see a good deal of the antischistosomal scheme in operation and had opportunities to study the disease itself I have set down below some of my impressions and some of the information I obtained in the hope that this monumental modern struggle against an ancient disease will interest and excite you as much as it did me

Clinical

The development of the signs, symptoms, and complications of *S japonicum* schistosomiasis has often been described, and, on the whole, most of the advanced cases I saw conformed to the expected patterns There were, nevertheless, numerous interesting points- which were emphasised by our Chinese colleagues

EARLY CASES

It was surprising to find, even in heavily endemic areas, patients with relatively recent infections, in whom a single short period of exposure to cercariæ could be clearly ascertained Many of these early cases had high irregular fever Some had diarrhœa but others experienced no gastrointestinal symptoms except anorexia Tenderness over the right upper half of the abdomen was common and in some cases the liver was tender and easily palpable one or two fingerbreadths below the costal margin The results of " liver function " tests were usually within normal limits

The clinical condition became very severe in some cases soon after the onset, with high intermittent or remittent fever, a notably enlarged and tender liver, and the development of a typhoid-like state A few developed cough and mild pulmonary changes

Early cases usually responded well to intravenous potassium antimony tartrate therapy Some, however, developed temporary pulmonary lesions during treatment which could be identified clinically and radiologically and which resembled in many respects those reported in other schistosome infections The clinical picture is familiar to Chinese physicians but is probably not so well known elsewhere It may therefore be of interest to summarise an example recently described by Dao Chin and others (1956)

The patient was a 16-year-old boy admitted three months after exposure to infection He had had irregular fever for ten days There was some tenderness in the right upper abdomen, but otherwise physical examination, including X-ray of the chest, revealed nothing abnormal, *S japonicum* ova were found in the stool The fever subsided slowly under potassium antimony tartrate therapy, but on the thirty-fourth day of treatment (after a total of 0 96 g of the drug) fever reappeared and the patient developed paroxysms of coughing without sputum There were some rales over the bases of the lungs and X-ray of the chest revealed extensive bilateral miliary lesions, especially in the lower lung lobes The patient did not feel ill and spontaneous recovery took place after a few days Six weeks later the lesions were still present but clearing

The characteristic features of this syndrome, which also appears in chronic cases, were the fever and cough developing towards the end of antimony therapy, the miliary infiltration and patchy consolidations in the lungs, the continued well-being of the patient and the self-limited course These peculiar pulmonary changes are believed to arise from fresh dissemination of ova to the lungs or from allergic activation of existing circumoval lesions

The severe pulmonary complications which occur in late *S mansoni* infections and lead to cor pulmonale seem to be rare in *S japonicum* infections even in cases with extensive hepatic and splenic involvement

COMPLICATIONS

Gastrointestinal complications are common in late japonica schistosomiasis, The lesions, which include polyposis, hypertrophy, and fibrosis of the colon and rectum, are similar to those seen in *S mansoni* infections The same is true of the liver and spleen involvement The cases I saw in the Endemic Diseases Hospital in Shanghai, for instance, closely resembled those distressing examples of late *S mansoni* infection so common in lower Egypt

The abdomen was distended with fluid and the superficial collateral venous vessels were very prominent (fig 1) The liver was usually large and firm but occasionally not enlarged The spleen was invariably enlarged, sometimes enormously so There was extensive œdema of the legs and the back

In cases associated with fibrotic changes in the liver, portal hypertension had developed with extensive abdominal collateral circulation Varicose œsophageal veins could often be demonstrated radiologically, but hæmorrhage from these vessels was apparently relatively infrequent Severe and catastrophic bleeding did sometimes occur, however, usually from rupture of varices of the basal gastric veins

These advanced signs were found in young to early middle-aged adults with long histories of exposure to infection, stretching in some cases over many years Most of the patients were

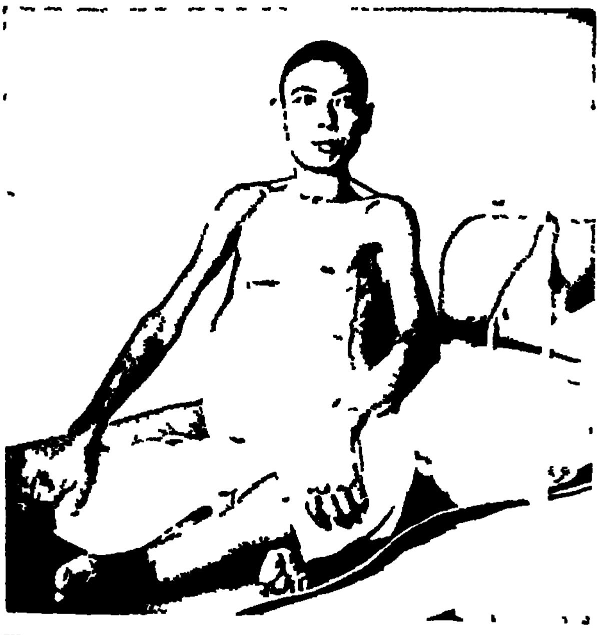

Fig 1—*S japonicum* infection with hepatic cirrhosis, portal hypertension, and ascites. Note the prominent superficial veins.

men, probably because of their greater risks of exposure There was no satisfactory information about the relation between the development of the complications and the intensity of the infection

Similar liver damage and fibrosis with ascites and portal hypertension and enormous enlargement of the spleen occur in older children, sometimes associated with pronounced dwarfism and retardation of sexual development Dwarfs of this sort were in evidence in several of the rural treatment centres I visited in the highly endemic areas Some had shown considerable improvement with antimonial treatment

The pathogenesis of liver lesions is still not fully understood, but the indications are that egg deposition plays a more significant part than the presence of the adult worms Thus, bisexual infections in mice and rabbits have been shown to produce much more severe pathological liver changes than unisexual infections, and intrahepatic injection of eggs more serious effects than injection of adult worm extracts, including infiltration of the connective tissue of the portal tracts and periphlebitis of the portal venules Changes in the vascular pattern of the portal tracts such as described by Bogliolo (1957) in human *S mansoni* infections have not been recorded

THERAPY

No entirely satisfactory chemotherapeutic agent with suitably low toxicity and high efficiency has yet been discovered

There is general agreement that the best results are obtained by the parenteral administration of trivalent antimonial compounds, of which potassium and sodium antimony tartrate are considered the most effective and are most commonly used These drugs are toxic and serious side-effects may develop even with carefully graded dosage The therapeutic activity and toxicity of a given course of treatment have been found to run parallel to the amount of antimony administered Contrary to widely held European views, no difference in toxicity has been observed between the potassium and the sodium salt, the former of which is in general use

Certain other antimonials, such as antimony gluconates, citrates, and guanides, are also active against the infection but for reasons of expense or toxicity are not favoured clinically

The results of oral therapy have not been encouraging Potassium antimony tartrate is the only antimonial which has been found to have some effect by this route (about 60% of its parenteral activity) Lucanthone (' Miracil D ') and certain acridine derivatives have been found ineffective clinically and experimentally

Studies in animal infections have indicated that the duration of the infection has little influence on the therapeutic effect of potassium antimony tartrate The interruption for a short time of a course of therapy and its subsequent completion has no obvious effect unless the interval is long On the other hand, full dosage given a long time after an inadequate course is not always effective, suggesting the development of some drug resistance

The necessity for better and safer drugs has led to extensive research in which many natural and synthetic compounds have been examined either clinically or in laboratory infections in mice, rabbits, or dogs In animal infections the most active antimonial has been found to be ammonium antimony gluconate, but this compound, which has about the same toxicity as potassium antimony tartrate, has not yet come into extensive use Compounds containing mercury, tin, and acridine dyes have proved largely ineffective So have derivatives of the diaminodiphenoxy-heptanes and hexachlorethane, a drug successfully used by the Russians for the treatment of opisthorchiasis

TREATMENT OF JAPONICUM INFECTIONS

Length of course (days)	Total dosage mg per kg body-weight)	Method *	Relapse-rate † (%)
1	8	3 doses, one every 3 hours	60
3	12	1 dose every 12 hours	32
7	15	1 dose daily	15
20	25	1 " "	15
25	30	1 " "	16

* In the 1-day, 3 day, and 7-day courses the drug was made up as a 1% solution in 25–30% glucose In the longer courses the glucose was sometimes omitted Each dose was given very slowly Maximum single dose 20 ml of 1% solution

† Techniques described under the section ' Results '

Chinese native herbs have been tested in laboratory animal infections and in in-vitro experiments against artificially cultured adult schistosomes Of some 200 examined, several, including the chrysanthemum, have shown some activity Clinical trials of these drugs are being organised mostly in the treatment of severely complicated cases

Details of Therapy

Courses of antimonial drugs used in the past have had the great drawback of keeping the patient too long from his work Attempts have been made, therefore, to reduce the length of treatment to an effective minimum Clinically and experimentally, intensive therapy, such as that devised by Alves and Blair, has been found very toxic and less effective than longer courses It has been discovered recently, however, that satisfactory results can be achieved by reducing the standard twenty to twenty-five days' course of therapy to a week This technique has resulted in a great saving of time and has proportionately reduced the immobilisation of the working patient to a period he is prepared to accept, thus leading to more efficient therapy and fewer relapses

Some of the dosage regimes which have been examined are detailed in the accompanying table The figures are based on the results of a single experiment carried out in hospitals and clinics and involving over 5000 cases of active *S japonicum* infections The therapeutic agents were potassium or sodium antimony tartrate given intravenously

In the field the therapeutic courses most generally used now are the seven-day and twenty-day regimes Presumably the former will become the standard technique

Results

In the above investigation, stools were examined for *S japonicum* eggs before, during, and after treatment, by hatching and sedimentation methods In some cases rectal biopsy was also performed With successful treatment eggs in the fæces became fewer about a fortnight after commencement of therapy and disappeared during the fourth week Early indications of success were the passing of opaque eggs which would not hatch, or the hatching of miracidia which did not survive beyond a few minutes In the follow-up, groups of three successive stools were examined every three months for a year after treatment

As will be seen from the table, the very short intensive courses were not as effective as the longer lower-dosage regimes Of the cases which relapsed, 70% again passed eggs within three months of treatment and 85% within six months Examination beyond six months revealed only a further 3% The routine follow-up recommended was therefore the examination of three successive stools at three and at six months after treatment, or, as a minimum requirement, at six months " Cure " was defined for practical purposes as being egg-free after twelve months It is realised, of course, that this may not be an adequate definition in some cases but it is believed to cover most

Side-effects of Potassium or Sodium Antimony Tartrate

Immediate toxic effects are often severe and occasional deaths occur.

In the one-day and three-day intensive courses side-effects were notable. Severe anorexia developed early and nausea and vomiting were common. A short period of dry coughing frequently appeared during the injection of the drug or immediately afterwards.

In the seven-day course, there was often pronounced anorexia and nausea and vomiting which appeared about the third day and persisted until the finish of the treatment. Coughing was usual.

In the longer courses, in which the dosage was built up more slowly, similar toxic effects developed and reached their maximum about the eighth day. Side-effects were less common and less severe in patients under 16 years of age.

Similar immediate toxic effects were prominent with all the other active antimonial compounds tried. Exfoliative dermatitis occurred in a few cases in the later stages of treatment.

Treatment of Complications

Patients in advanced schistosomiasis are treated in general hospitals or regional centres. On admission they receive as a routine a high-protein diet and appropriate vitamins for a week or more while diagnostic procedures are carried out. Cases with obvious hepatic involvement are placed on a low-salt diet.

Certain severe cases, especially in the hepatic group, are selected (at their own request) for treatment with Chinese herbs, some of which cause watery catharsis with considerable relief of œdema and even of ascites. I was told that cases which responded in this way were afterwards given standard antimonial treatment, sometimes successfully. So far as I could ascertain the clinical use of Chinese remedies for schistosomiasis was at present confined to these complicated cases.

Portal hypertension, which develops in chronic or frequently reinfected cases in early adult or middle age, is regarded as the most severe complication.

Although in such patients ascites is common and often severe, paracentesis is rarely practised except for bringing essential immediate relief, since it has been found that the frequent removal of ascitic fluid often establishes a " chronic " state in which regular drainage becomes necessary. Attempts are made, however, to reduce the fluid by salt-free diets and diuretics.

Hepatic coma and mental symptoms are common. Reduction of protein intake sometimes leads to rapid and dramatic improvement in such cases.

Hæmatemesis and melæna are serious hazards, the former arising from rupture of varicosities in the gastric rather than œsophageal veins.

Hepatic disturbances and hypersplenism have been relieved by various surgical techniques. Thus, splenectomy has been found beneficial in many cases, and is usually followed by full courses of antimonials.

Cross-circulation techniques including splenorenal or porta-caval anatomosis and ligature of the hepatic artery have been carried out for the relief of portal hypertension. Some cases have benefited greatly by these procedures and have lived for years after operation. The operative mortality is however still high.

The prognosis of complicated hepatic cases on the whole is poor, whatever is done for the immediate relief of symptoms. Nevertheless, many of the intermediate cases, even those in which severe hæmorrhage has occurred, are temporarily benefited by treatment.

DIAGNOSIS

In early cases the diagnosis depends on the discovery of the ova of *S. japonicum* in the fæces or in scrapings or biopsy specimens taken during proctoscopy.

Eggs in fæces.—The ova are revealed by examination of stool smears, by stool sedimentation methods or by the hatching technique in which a sample of fæces is allowed to come into contact with water so that miracidia hatch out. Comparative studies of these methods carried out on a very large scale have shown that the direct examination of the stool is the least, and the hatching technique the most, reliable. Thus, in one study involving over 5000 patients, a single examination of the stool by the hatching technique disclosed 1500 more positives than the sedimentation technique.

Examination of successive stools also increases the overall chance of finding eggs. For instance, in a group of 980 cases in which ten consecutive stools were examined, 480 were found positive at the first examination and 750 by the seventh. Thereafter further examinations revealed very few more positives.

Rectal biopsy.—All clinicians seem agreed that the examination of rectal biopsy material considerably increases the chance of positive diagnosis even when there are no obvious lesions. To facilitate immediate control of accidental hæmorrhage following biopsy, specimens are taken from tissue not more than 6 in. in from the anus.

Antigens similar to those used for intradermal tests are used to determine the presence of complement-fixing bodies in the sera of early cases, late cases, and cases at various periods after successful treatment.

With suitable antigens (including the " liver-ova " antigen referred to below) positive reactions are obtained in the majority of active infections (85–90%), and in a smaller proportion of treated cases. False positives are rare, even in cases in which other trematode infections were present. The test has some prognostic significance. For instance, in a series of examinations using adult worm protein-fraction as antigen, positive reactions were obtained in 15 out of 15 cases tested three months after treatment, in 7 out of 9 six months afterwards, in 5 out of 11 up to two years afterwards, and in 2 out of 7 cases examined two to four years afterwards.

Other successful serological tests which are being studied, especially in experimental animal schistosomiasis, include precipitin reactions and cercarial (C.H.R.) and miracidial fixation. The latter are said to be in some respects more sensitive than complement deviation but are not in general diagnostic use.

Diagnosis in Mass Surveys

Direct stool smear examination, sedimentation, concentration and hatching, rectal biopsy, and serological methods are all unsuitable for large-scale surveys. In the last few years therefore much attention has been directed to the study of intradermal antibody-antigen reactions in all stages of the infection before and after treatment. Most extensive research has been carried out by Chung (1956) and others, for instance, on the activity of antigens made from adult worms of either sex, from extracts of polysaccharide and protein fractions of adults, from eggs, miracidia, cercariæ, and from snails. These workers recently prepared from the livers of laboratory-infected rabbits a powerful antigen which has been mass-produced and used in screening the population of something like 60 million believed to be at risk to schistosomiasis.

The Chung antigen is prepared as follows:

> Rabbits are infected with cercariæ, and are killed six to ten weeks later. The livers, which are filled with pseudotubercles containing ova, are homogenised after removal of adult worms, and dried. A 1% saline extract of this material is made up with 1 in 10,000 parts of ethyl mercuric thiosalicylate as a preservative, and can be stored in the cold for several months without loss of activity.

The skin test is carried out by the intradermal injection of 0.1 ml. of antigen diluted to 1 in 1000 or 1 in 2000. The control is an intradermal injection of 0.1 ml. of saline containing the same quantity of preservative. Readings are made about fifteen minutes after the injection. A positive reaction is shown by the appearance of a weal with pseudopodia, surrounded by a zone of erythema The reactions subside after an hour

The diagnostic value of this skin reaction in individual cases is limited by cross-reactions which may arise in infections with other trematodes, notably paragonimus, clonorchis, and fasciola (from the adults of which active antigens may also be made) To some extent this difficulty may be overcome by determining the reactions of the skin to increasing dilutions of the several specific antigens until the point is reached at which the reaction to the schistosome antigen remains positive and that to the others has become negative In mass surveys in areas where the distribution of the other flukes is approximately known, however, a positive specific intradermal reaction to the schistosomal antigen is reasonably considered significant

The results of intradermal reactions to the liver-ova antigen correspond to those of complement-fixation reactions with the same antigen, in that positives occur in a very high proportion of active infections and are progressively fewer after treatment Similar results so far as intradermal reactions to specific antigen are concerned have been reported in *Schistosoma hæmatobium* infections by Sherif (1956) and others, but Oliver-Gonsalez (1954) observed the reverse with a *S mansoni* egg antigen Chung suggests that the Chinese antigen owes some of its activity to the liver tissue from which it is prepared

Methods and Technique of Schistosomiasis Control

FÆCES AND SCHISTOSOMAL EGGS

In the campaign against schistosomiasis emphasis is being laid particularly upon limiting the dissemination of infective eggs by controlling promiscuous defæcation and by storage of fæces for up to a week before use in the fields, in order to allow the ammonia generated to destroy the ova, which might otherwise survive for several months The cooperation of the people has been sought by propaganda expounding the social and sanitary advantages of fæcal control and by official payment for night-soil, pro rata, according to age (? on a basis of weight for weight)

In most villages and cooperatives today, each family has its own collecting-pots which are emptied daily into common earthenware tanks in the village compound The communal pots are sealed when full and the contents are removed after the requisite time and transferred to open tanks in the fields for immediate use The collection of fæces in this way, together with subsequent properly supervised washing of individual family and community vessels, avoids one of the principal dangers of the past, when washing of night-soil containers in the ditches and canals was a common means of spreading the infection to the local snails

The dissemination of infection by human fæces is being brought under control in this way, but a major problem still needing a solution is the conservation of animal fæces

This is particularly so in domestic animals which have been shown to be a dangerous source of infective eggs, especially cows and the ubiquitous water-buffaloes, which wallow in every irrigation ditch (the main unsavoury homes of the intermediate host) Moreover, some animals, including the coprophagous pigs, easily become infected and pass eggs in the fæces, or are capable, like dogs, of passing viable ova after eating infected material Since the water-buffalo is the most important of all domestic animals, its susceptibility to infection is of primary significance and has to be taken into account in the control of schistosomiasis Medical and veterinary workers are collaborating to find practical means of reducing such animal infection and controlling the dissemination of suspect fæces

CONTROL OF SNAILS AND CERCARIÆ

The prevailing methods used for killing snails are based on the results of years of concentrated research which have been going on in the field and laboratories, such as those of the Shanghai Institute of Parasitology, where the bionomics of oncomelania from all parts of the country have been studied, and their reactions to various physical and chemical environments examined

Infection of Snails

The breeding habits of oncomelania have been carefully watched with a view to finding biological techniques for limiting the snail population in the field It has been found that mating takes place through the year but is at a minimum in the spring and early summer and at a maximum in the early winter Hibernation starts in the autumn Egglaying and hatching also go on throughout the year, but the latter is slowed by cold In the laboratory the adult snail develops in about six months

Snails are most numerous in wet, moist soil near water and thick grass The population is densest in irrigation ditches and becomes progressively thinner along the banks of rivers and canals, in rice-beds, and in the paddy fields Isolated pools of water are less important breeding-grounds The mortality-rate of uninfected snails in the field does not change much with the seasons but that of infected snails increases in the summer and decreases in the early winter The mortality of both is higher in dry conditions

The activity of snails has been studied under many circumstances They are most active at night and crawl at a rate of about 3 metres in a month They are found on land mostly within $1^{1}/_{2}$ metres of the water surface, fluctuations in the level of which appear to make little difference

Naturally infected snails are found throughout the year, the highest infection-rate is in August-September Using cercariæ from rabbit-liver ova, laboratory infection can be achieved in about 60% of many local strains of oncomelania at temperatures of 21 to 36°C, but there is some variability in the susceptibility of snails collected from different districts in the endemic area Cold conditions very considerably reduce the infection-rate Planorbiid and other genera so far examined have not been infected

Anticercarial Measures

Cercarial discharge from snails occurs earlier after infection in a hot environment than in the cold Snails may remain infected and capable of discharging cercariæ for over two and a half years

Cercariæ from captive or naturally infected snails remain infective for up to three days when suspended in water, provided the temperature is low There is no difference in infectivity towards mice amongst cercariæ collected at various times of the year under natural or laboratory conditions

Although human infection most commonly takes place as the result of penetration of cercariæ through skin exposed to the water of canals and irrigation ditches (fig 2), it can also occur through contact with minute droplets Dew-drops in some paddy fields have been found to be charged with active infective cercariæ in very large numbers It is not yet known how significant this path of infection is, but it clearly

Fig 2—Exposure to cercariæ in canal water

has to be considered in attempts to limit the spread of infection, particularly in local areas in which human or animal defæcation has not yet been adequately controlled

The destruction of cercariæ and the prevention of their penetration through the skin have been studied by means of various chemical techniques and the use of protective clothing Under standard experimental conditions in which the shaven bellies of white mice are exposed to water containing known numbers of cercariæ, over a hundred test substances, including native herbs, have been examined by applications to the animal skin of oils, ointments, infusions and solutions Mixtures containing Tung oil have been found effective in protecting mice and have been used in the field in the form of repeated applications to exposed areas of skin Many substances which kill snails have also some antimiracidial and anticercarial effect Such methods may have some temporary value but are regarded only as palliative

Chemical Control of Snails

The toxic action of many substances in the form of solutions, emulsions and powders has been studied, including copper sulphate, paris green, calcium arsenate and arsenite, calcium cyanamide and superphosphate, wintergreen oil, and phenol

Copper sulphate is a good molluscicide in a dilution of 50 parts per million, at which concentration most of the others are ineffective The copper salt is expensive, however, and relatively inactive when mixed with mud or dirty river-water The compounds most commonly used on a big scale are paris green and calcium arsenate (or arsenite) The former is effective but slow as a spray in concentrations of 9 0 g per square metre but is unfortunately harmful to animals and rice crops The latter is freely used as a spray in concentrations of 6 to 12 g per square metre in areas away from livestock or humans

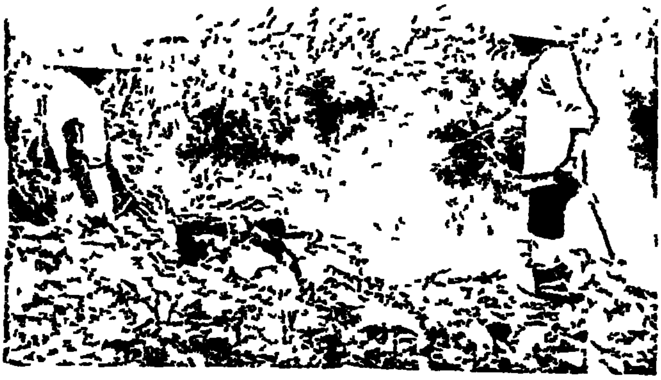

Fig 3—Ditch spraying with calcium arsenate

Synthetics such as dicophane (D D T), gammabenzene hydrochloride dimethylphthallate and sodium pentachlorophenate, and substitute phenols, such as sodium tetrachlorophenate and diethylparanitrophenyl thiophosphate (E 605) have also been examined Of these the latter group are most active molluscicides, but some of them are unfortunately extremely toxic to fish and are ineffective in the cold, their activity is notably reduced by contact with mud or dirty water

Nearly six hundred Chinese herbs have been tested, of which fewer than twenty have any appreciable molluscicidal effect in concentrations of 1% or lower For example, infusions and oil emulsions of croton have been proved successful under laboratory conditions but considerably less so in the field So far no indigenous drug has been found economically satisfactory for use on a large scale

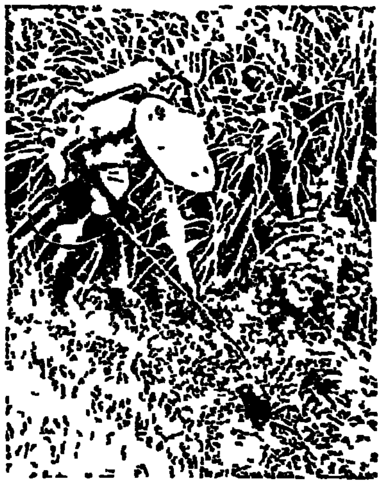

Fig 4—Using a petrol flame-thrower on the banks of ditches

Physical Methods of Killing Snails

During the summer large numbers of snails are found on land within $1^{1}/_{2}$–2 metres from the water line Spraying, burning, and scalding of this area are all effective killing measures and are widely used in villages and other occupied regions The cheaper technique of spraying with poisonous chemicals, such as calcium arsenate, is restricted to the ditches and canals in the fields (fig 3)

The burning of the grass on the banks of small creeks and ditches is carried out by means of portable petrol flame-throwers carried on the shoulders or on wheelbarrows The banks of larger canals and streams are scorched by flame-throwers mounted on punts, and burning carbon monoxide gas made on the spot (figs 4 and 5) This process is slow but effective, as I could see for myself when I joined the hordes of village children picking up roasted snails in the wake of the operators

Snails embedded in mud are not destroyed by burning or spraying and have to be killed by other means, the best of which is some form of ditching

Snails are normally concentrated within 10 cm of the surface of the mud near the water level, if they become buried deeper they suffocate Farmers are therefore encouraged in the winter months to concentrate on the time-honoured better-

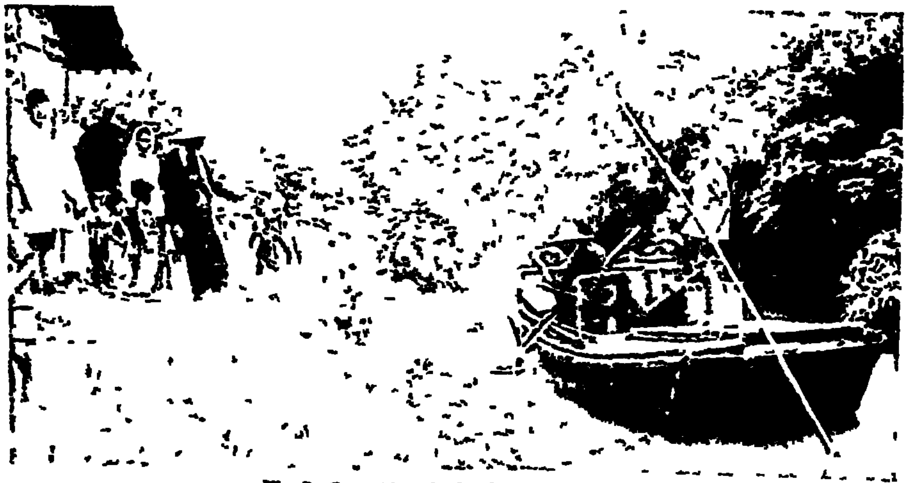

Fig 5—Scorching the banks of a canal

ment of their canals and ditches by manually removing and burying the snail-containing mud In this way the banks of waterways are cleared yearly of weeds and the ditch beds are deepened or replaced A recent field experiment showed that the more thorough process of filling in the old ditches and digging new ones was the most effective and accounted for almost all the snails buried in the mud The simpler process of clearing overhanging grass and covering one side of the ditch with soil from the other is less effective, but removal of the superficial layers of earth from both sides and storage or burial of this material is a highly efficient technique, 70% of the snails dying within a month and 98% in three months

Simple methods of this kind are now being used on a large scale, especially during the winter, after the killing of active snails in the summer by means of burning or spraying The effectiveness of these procedures was demonstrated recently in one experimental area in which the population of snails was reduced by 98% twelve months after treatment (filling in and replacement) of 15 km of ditches

Other physical methods of control which have proved valuable in appropriate areas are reclamation of "low or flood land by the erection of embankments and the subsequent removal of the overgrowing grass", and in some cases the conversion of reclaimed rice fields for the growth of other crops These more extensive operations have been completed by the antischistosomal organisation in collaboration with other departments and Ministries They illustrate the combined operations necessary for the successful outcome of the nation's all-out totalitarian attempt to "liquidate" the threat of schistosomiasis to the future of the new China

The combination of burning and spraying plus ditching is already having a considerable effect on the population numbers of the intermediate host This, together with the mass-treatment campaign which is already in active operation, cannot fail greatly to reduce the endemicity of schistosomiasis within the afflicted areas When suitable methods for the prevention of infection in the domestic-animal reservoirs have been evolved, the disease should be brought swiftly under control

My thanks are due to my many Chinese friends for valuable help and advice

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Medicine and the Law

Jury's Responsibility in Assessing Diminished Responsibility

At the trial of a young man on a charge of capital murder by shooting, one of the defences put forward was that he was suffering from diminished responsibility within the meaning of section 2(1) of the Homicide Act, 1957 Although there was evidence which could have justified the jury in finding that it was a case of diminished responsibility, it was not such as to compel them to come to that finding According to the evidence the man had an intelligence quotient of 110 Copies of section 2(1) were handed to the jury so that they could see it, and the judge, summing up, read the section to them, told them that it was for them to decide whether or not the man was suffering from such an abnormality of mind as substantially to impair his mental responsibility, and then reviewed the evidence on that issue The jury convicted the man, who was sentenced to death On his appeal it was argued for him that the judge should have given the jury a direction as to the meaning of the expressions "abnormality of mind" and "mental responsibility" in the section, and that, since counsel for the prosecution in his speech to the jury had submitted that "abnormality of mind" was limited to a deficiency of intelligence and that certain conditions of which evidence had been given—emotional instability, temperamental instability, psychopathic personality, gross personality disorder, immature personality, and abnormality of control of the emotions—could not come within the expression, the judge should have ruled upon those submissions For the convicted man it was contended that "abnormality of mind" was not equated with deficiency of intelligence but that a person suffering from those conditions and unable to control his emotions came within the section

The LORD CHIEF JUSTICE, giving the judgment of the court, said that a judge could do no more than call the attention of the jury to the exact terms of the section which Parliament had enacted and leave them to say whether upon the evidence they found that the case came within the section or not

When Parliament had defined a particular state of things, as they had defined what was to amount to diminished responsibility, it was not for judges to attempt to define or redefine the definition It was a question of fact in any particular case for the jury to decide The conception of diminished responsibility was borrowed from the Scottish common law which recognised that a man might be not quite insane but a borderline case and that that was the sort of thing which amounted to diminished responsibility Where a defence of insanity was set up it had always been for the jury to find whether or not there was a disease of the mind and that could only be found by listening to the medical evidence and the facts of the case and coming to the conclusion whether what the defendant did was the act of a sane or an insane man So here all that could be done was to read the section to the jury and say "these are the tests which Parliament has said are to be applied You are to consider whether the defendant has abnormality of mind"—and his Lordship did not know how that was to be defined because it was very difficult to say what was a normal person—"whether arising from a condition of arrested or retarded development of mind or any inherent cause or induced by disease or injury If you find any of those matters in the evidence, you may find a verdict of manslaughter and not of murder"

In English law the expression "What would be the act of a reasonable man?" was very common, but his Lordship did not know of any definition of a reasonable man, The jury had to decide for themselves whether the action in question was the action of what they would call a reasonable man and so here the matter was entirely one for the jury The judge had put the case in the only way it could be put and it was not his duty to enter into metaphysical and philosophical distinctions between intellect and emotion The appeal was dismissed

REGINA *v* SPRIGGS *Court of Criminal Appeal* Lord Goddard, *C J* Hilbery and Salmon, *J J* Jan 14, 1957 Graham Swanwick, Q C and C H Durman (registrar, Court of Criminal Appeal), R K Brown (Director of Public Prosecutions)

J F LAMB
Barrister-at law

In England Now

A Running Commentary by Peripatetic Correspondents

ALTHOUGH we always say what we mean, we do not invariably mean all that we say, but on this occasion it is with no negative reservations that we welcome the appearance of a new journal, the *Journal of Negative Results* (*J neg Res*), and hail it with the freshly minted phrase that it "fulfils a long-felt need" Indeed, so much material is awaiting publication in this field that the editorial board have adopted a strict policy, for the time being, papers are only accepted if statistical analysis of the results gives $P > 0 9$ Later, the editors hope to be able to include papers whose results are statistically significant, but are otherwise meaningless

For the opening number the editors have secured a distinguished panel of contributors, but diffidence in face of the laws of libel forbids us to mention their names The papers include an interesting historical article on Medicine in Laputa, and there is an essay on the negation of negation The journal has the distinguished format which we have come to expect from the Erewhon University Press, but we hope that in future issues the blank cover will be replaced by something more misleading The motto of the new journal is taken from Faust—"Ich bin der Geist, der stets verneint" We wish the editors well in their new venture, and hope to assist them with papers from time to time

* * *

We had known for some time that the Royal Ontario Museum in Toronto was putting on one of the largest exhibitions of English silver ever assembled and that it was being opened by the Governor General This made the opening a social as well as a cultural highlight, and 1500 of the Best People were invited But, of course, in a population of only 16 million it is not really selective to be one of the 1500, and so 300 of the Very Best People had been asked to dinner before the opening But 300 is such a crowd, so 40 of the Really Very Best People were going to a cocktail party before the dinner before the opening The big problem was how to face my friends on Monday because I had not been invited even to the opening, and some of them might be one, two, or even three up In a flash of genius I got myself admitted on the previous Friday, to the press showing (on the grounds of being a *Lancet* Peripat)

The press show was rather like going to see a film star in his dressing-room, because the display had not yet been completed. There were great hunks of silver lying about all over the place, and knee-deep in candlesticks, mirrors, sauce-boats, and salvers there were policemen with guns They looked a little sheepish, it did seem pedantic to guard the stuff when the museum staff were continually casually mislaying objects worth a hundred thousand dollars Also around the place, among my temporary press colleagues, were the art critics who had been reading that *Penguin* book about silver This gave them the chance to say "surely that's a trifid spoon?" The label confirmed this, but it plunged me into humiliation I did not know that one ate trifids with a spoon. Ah, here is a trifid fork So next time I am offered trifids at a banquet I shall nonchalantly pick up a spoon and fork, and not use a knife—if I can find out in the meantime how to recognise trifids

I found that many of the still open display cases contained notes pencilled on paper to show where the pieces were to go Here is one that says "the good one" That is the height of patronage, it seems to me Here is a solid silver picnic set, of all things, made in 1680, with knife, fork, spoon, condiment box, and nutmeg-grater There are 13th-century spoons with no nonsense about them and rococo work with a lot of nonsense, graceful sauce-boats and curly salt-cellars, the Everest cup and the Coronation cup There is a silver bathtub and an aspidistra pot, both labelled as wine-cisterns

By now I was getting pretty blase about silver and was baffled rather than impressed by a mirror belonging to the Duke of Brunswick This is about as big as a bus, with 3-D coats of arms all over and a couple of silver chairs to match Another pencilled instruction catches my eye. "Put the *art nouveau* thing here" That makes my day "The *art nouveau* thing"—so casual, with a hint of knowing what *art nouveau* is I'm all set for Monday now "Oh, are you going to the opening tonight? I saw the show last week—you really must look out for a rather nice *art nouveau* thing they have there "

* * *

My two-year-old was lying in his bath and probably for the first time his eye fell on his umbilicus There was a horrified expression in his eye and he called out, "Mummy, Mummy! Look! Hole! Mend!"

* * *

The lumbago-sciatic shooting now being open[1] we can look forward to some smart exchanges, for the subject has long been controversial Even in Shakespeare's time the widest extremes of view were evidently held The remark of the 1st Gent to Bawd "How now! Which of your hips has the most profound sciatica?" (*Measure for Measure*) shows the ribald back-slapping approach as opposed to Sycorax's serious and intensive treatment of Ariel by twelve years manipulation in a cloven pine without anaesthetic (*Tempest*) Rigorous though this regime may have been, it undoubtedly restored the patient the full use of his exceptional mobility

* * *

THEBES

It was evening when we reached the village,
After the long drive over hot, dusty plains
There, still sharing some needs with ancient wayfarers,
We stopped for bread and water,
So learned by accident, believing it many miles distant,
That this was Thebes

Could this be Thebes, a city of kings?
We might have known, out on the plain
Where corn ripened and the kites and vultures scavenged
And pitiless heat beat down,
That there was the inevitable setting
For Antigone Almost we passed her,
Still pitifully scraping a grave for her dead brother
Out there nothing has changed
But here in the streets, who remembers doomed Œdipus?
Who has even heard of successful Creon?
Yet this was, this is Thebes
Here now, here ever,
Left by the long since ebbing tide of history and myth and drama,
The grey-haired elders, the perennial chorus,
Sit sipping their drinks, savouring the flavour of life and commenting on it
At small tin tables on the shady side of the street

There are locked, rusty gates nearby (the elders will direct a pilgrim)
Where carved, broken stones,
Mortal relics of an immortal past,
Lie in a sleepy garden
Petunias and hollyhocks and flowering trees
Wave them a careless tribute of royal colours
Heroes and lovers, human or sired by gods or dreamed by poets,
Sleep alike their long sleep
While hawks and doves nest neighbouring among crumbling masonry
To this garden we came, rare visitors
The custodian, shrunken, wrinkled, brown,
Unordained priest of a self-consecrated shrine,
Welcomed us, stroked a stone lion for us,
Intoned the names of the muses, spelt out caressingly
A little tombstone of much loved Demetrius
He gave us each on parting a rose and a sprig of mint,
But these we lost, and now have nothing left of Thebes
Except the ghost of a perfume and a memory

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[1] *Lancet*, Jan. 4 1958, p 20, Jan. 11, 1958, p 107

Letters to the Editor

THE "LADDER"

SIR,—In giving evidence before the Royal Commission last week I wanted to put in a word for senior registrars who by their energy and intelligence had climbed the ladder at their medical schools, only to find too often that it led nowhere

Let me explain what I mean by this ladder The ambitious boy who enters a medical school singles himself out by winning prizes in the annual class examinations, and later by obtaining honours or perhaps a gold medal in university examinations After qualifying he must compete for a series of posts, and all the time the competition grows fiercer Indeed he may be eliminated before he is ready to take the last hurdle, that of senior registrar, because he has failed in the examinations for the higher degrees In this manner, from the survivors of this cut-throat struggle, the hospital staff is elected And the young consultant so chosen is now singularly efficient, not only on account of the severity of the competition but also because he has gone through a period of intensive training, which often extends, according to the Royal College of Physicians, over a period of ten, fifteen, or even twenty years after qualifying In this way he has accumulated a store of knowledge and experience which gives him a great pull over those who have not had the advantage of this discipline

But will this last? Material rewards are of course not the only incentive, but in the past the incomes enjoyed by men who were successful in consulting practice led students at the top of their year to attempt to climb this ladder But these inducements have been whittled away and if these men can no longer look forward to an adequate reward for their labours, they may plan their lives differently They know that now they will have to face long years of training after they have qualified, years of comparative penury, years of uncertainty, because in the end success is far from assured And they know too that in the event of failure no alternative career in general practice may then be open to them at their age The waiting years have been unduly drawn out, and the disparity between the number of consultant vacancies and the number of senior registrars competing for them is such that men are beginning to ask "Is the game worth the candle?" Already there has been a sharp fall, both in London and in the Provinces, in the number of applicants for the post of registrar The writing is on the wall for those who can read

I had hoped that if I could describe accurately the means used by hospitals to sift candidates for election to their staffs I might be able to convince the members of the Royal Commission that the senior registrar who had emerged successfully from this ordeal ought not to be thrown lightly on the scrap-heap, that his achievement was worthy of some reward Moreover while I was speaking of the senior registrar I had at the back of my mind the whole question of consultant recruiting Alas I was met only by doubt whether there was in fact any such ladder, that all men in our calling are equal If I had been wise I should have left it there Others in good time would have taken up the task of explaining how the consultant ranks are recruited But in the quick exchanges that followed I allowed myself to be drawn outside my argument I was asked in effect whether I considered the consultant a person apart, and only then did I tumble to the fact that my arguments for rewarding the man when he had climbed the ladder had been taken as critical and even derogatory of those who had never even made the attempt I protested I spoke of the "very high standard" of general practice as I had known it and of the "extreme ability" of many practitioners in my own experience But the damage was done

I was dean of a medical school throughout the twenty-five years I was on the hospital staff, with the exception of a few months in 1920, and it was my custom to spend about three-quarters of my day among my students I was completely engrossed in them as individuals, in their plans for the future, in their hopes and fears And I like to think that there existed between us mutual respect and even affection, certainly on my part there has been an enduring regard for their solid worth and good sense The overwhelming majority became general practitioners and I should be sorry if any of them were led to believe by the enterprise of the Press that I have changed and admire no longer the fine job they have made of their lives of service

London, W 1 MORAN

DEATH FROM POSTMATURITY OR INDUCTION OF LABOUR?

SIR,—Mr Gibberd (Jan 11) rightly points out that present methods of inducing labour are not entirely free from danger However, experience does not support his suggestion that the dangers of induction outweigh those of postmaturity in uncomplicated cases In a group where the dangers of postmaturity are relatively great (primigravidæ aged 25 or over) we adopted in 1953 a policy of routine induction in the 42nd week and began to use cæsarean section more freely, particularly if there are signs of fœtal distress, especially meconium in the liquor amnii This policy has been very successful in producing a marked reduction of perinatal mortality Dr Elizabeth Turnbull and I have published the relevant data elsewhere[1]

Midwifery Department,
University of Aberdeen DUGALD BAIRD

SIR,—I would like to present figures from the Obstetric Unit, University College Hospital, for comparison with those of Mr Gibberd

From 1952 to 1957 inclusive 386 patients (240 primigravidæ) were induced for postmaturity, mostly close to the 42nd week of gestation There were 20 cæsarean sections There were no deaths in this series attributable to the induction or to anoxia or asphyxia 3 deaths which occurred were

1952 Stillbirth, weight 7 lb 3 oz, 42 weeks Low amniotomy revealed meconium Fœtal distress developed 11 hours later and the fœtus was delivered by cæsarean section but failed to breathe Necropsy showed nutmeg liver, cystic adrenals, and a phæochromocytoma The mother, a primigravida, had rubella in early pregnancy and positive Wassermann and Kahn reactions

1956 Neonatal death Mother primigravida $2^{1}/_{2}$ weeks postmature Induction-delivery interval 98 hours, labour 20 hours Difficult forceps delivery, baby died 3 hours later Bilateral tentorial tear attributed to difficult labour and delivery of postmature fœtus with hard and unmouldable skull

1956 Neonatal death, at 23 hours from pneumonia Induction-delivery interval 68 hours Oxytocin infusion for 42 hours, forceps delivery This patient was not given antibiotic cover after the induction, and the pneumonia from which the fœtus died may have been contracted in utero

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[1] *Brit med J* 1957, ii, 1021

Factors which make the induction of labour safe for the postmature fœtus would seem to include

1 Routine antibiotic treatment for the mother from the day after induction until delivery [1]

2 Induction by low, in preference to high, amniotomy

3 Not delaying induction beyond the 42nd week

4 The use of oxytocin (not 'Pituitrin') intravenous infusion (not frequent small injections), with a tocodynamometer to assess the uterine response so that the infusion-rate can be suitably adjusted, to supplement or proceed amniotomy in all patients for whom the oxytocin-sensitivity test indicates that the uterus is insufficiently irritable to respond to amniotomy alone

5 Giving attention to early signs of fœtal distress and not allowing the labour or induction to be prolonged if there is meconium or abnormal slowing of the foetal heart-rate This entails 4-hourly observations on the fœtal heart—$^1/_2$-hourly if the maternal blood-pressure is raised, and $^1/_4$-hourly during oxytocin-infusion treatment [2]

These figures show that induction can be a safe and life-saving procedure by avoiding excessive postmaturity It can save more lives than Mr Gibberd gives even the perfect method credit for This may be because these babies have an average weight in the 8 lb region and good ability to survive provided they are saved from prolonged anoxia and the dangers of a difficult delivery In his opening sentence Mr Gibberd postulates anoxia as the basis of fœtal death in postmaturity Is it not possible that size and rigidity of the head could increase the danger of delivery too?

University College Hospital,
London, W C 1

C N Smyth

Sir,—Mr Gibberd's paper advances our knowledge regarding the management of postmaturity In trying to gain a familiarity with the problem I examined some 11,000 consecutive case-records I found that the stillbirth-rate rose steadily from 1 47% in patients delivered at the 40th week, to 9 3% when pregnancy had lasted 44 weeks or more In this latter group asphyxia was a *possible* cause of almost 80% of the stillbirths In half of these cases, however, death did not take place until labour had lasted more than 48 hours, and it may be argued that prolonged labour rather than postmaturity per se was the cause of the asphyxia, and further that the cause of death in some of these may well have been intrauterine infection of the foetus and not asphyxia at all

By a less lucid reasoning than that of Mr Gibberd I arrived at a similar answer—namely, that wholesale surgical induction of labour could not be expected to solve the problem I feel, however, that greater emphasis might be placed on the point that it is in the very group of patients we are trying to treat that induction is most likely to be unsatisfactory and dangerous

If, for example, we knew at the 41st week that, in the absence of interference, labour in a particular case would not begin for another 3 weeks, and if we made some attempt to explain why this should be so, we might suggest a mechanical reason such as malpresentation or disproportion, or we might say the cause was humoral in nature, or we might simply say that the uterus was not yet ready for action In any case we might hesitate before rupturing the membranes since in such a patient we would not be surprised to find that labour was delayed in onset and inert in character There is a considerably increased incidence of prolonged labour in postmature cases, and I believe the relationship to be one of common cause rather than of cause and effect The common cause may be mechanical or it may be humoral

When, to this contention, is added the consideration that it is not possible to preselect these cases, so that the operation must be performed unnecessarily in hundreds of others, the argument against induction of labour seems to be a strong one

Cæsarean section may well be the key to the problem, and if we could find a means of detecting the diminishing oxygen reserve of the fœtus before the onset of actual asphyxia, its value would be immeasurably the greater in that it would then be neither too often employed nor too long withheld

Nottingham

J M Gate

Sir,—I was interested in Mr Gibberd's article Is it not fairer to say, however, that the choice is not quite so clear as his title suggests? Most infants that are lost from postmaturity are lost, if the mother is not induced, by anoxia, and die, as Mr Gibberd points out, before, during, or immediately after labour But if the mother is induced, although induction is a hazard, the cause of death is still anoxia in most cases So the real choice is between death from postmaturity and death from postmaturity plus induction, the induction being a factor but not, necessarily, the main hazard

In our department we have practised surgical induction as a fairly rigid routine when the pregnancy has gone 14 days past the expected date as far as we can possibly judge During the past five years (1952-56) 607 consecutive surgical inductions have thus been done where the indication was simply term plus 14 and no other possible factor requiring induction was present Our total fœtal loss, both of stillbirths and neonatal deaths, was 15, but 4 of these had congenital abnormalities incompatible with life So there was a loss of 11 babies—or 1 8% All 11 (compare Mr Gibberd's table II) died from anoxia

Now, granting that surgical induction played some part, I nevertheless disagree emphatically with Mr Gibberd when he says that in uncomplicated cases it is, possibly, better to avoid the treatment of postmaturity altogether, rather than to embark on a rigid policy of prevention Can a loss of 1 8% over a large number of patients be lowered by those who never do a surgical induction for uncomplicated postmaturity? Mr Gibberd's figures (table I) show that at 43 weeks the infant loss is 2 8% and at 44 weeks 4 3% Why should it be assumed that these 11 babies would not have perished from anoxia if allowed to go on and on in utero until the natural onset of labour? We realise that even some of these 11 that we lost might have been saved by earlier intervention with a section, which is now our practice, according to the merits of the case, at the onset of meconium or the finding of scanty or absent liquor, both of which findings are hidden from those who have not ruptured the membranes

Marston Green,
Warwickshire

G S Lester

INFLUENZAL ENCEPHALITIS

Sir,—Dr Dubowitz's account (Jan 18) of two cases of infective encephalitis recalls a case in my practice

On Sept 20, 1957, a boy, aged 13, fell ill with aching, shivering, headache, and stuffiness of the nose He had no cough or pyrexia By Sept 26, deafness, due to eustachian catarrh, had developed, but there was no evident otitis media While his siblings and mother were in bed with influenzal symptoms and his grandmother delirious from influenzal bronchopneumonia, he became severely ill with shivering, sore throat, weakness of the legs, delirium, headache, vomiting, and cough At no time did I find any signs in his lungs His temperature was 104 F, face and eyes were bright red, and meningism was present (stiff neck and straight leg raising only to 30°) His temperature was normal, but he felt as though he was rotating, and as though iron bars were lying on his legs He had obvious nystagmus to both sides and past-pointing to the right No cranial nerves were affected Supinator- and triceps-jerks were not obtainable Biceps-jerks and knee-jerks were present and, on reinforcement, ankle-jerks On Oct 6 meningism was still present, on Oct 8 the tongue deviated well to the right, and on Oct 10 the palate deviated to the left

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[1] Bound, J P, Butler N R, Spector, W G *Brit med J* 1956 ii, 1191, 1260

[2] Dumoulin, J G, Martin, J D *J Obstet Gynæc Brit Emp* 1957 64 123

[3] Karn, M N, Penrose L S *Ann Eugen, Lond* 1951, 16, 147

I last saw him on Oct 14 when he was almost well, but still showed nystagmus He was treated symptomatically throughout

Though pathological tests were not made in this family, the general pattern was similar to that in other simultaneous cases in which influenza virus A was found on cultivation and by complement-fixation tests

Ilford, Essex R N COMPTON SMITH

RADIATION HAZARDS IN PELVIMETRY

SIR,—Dr Lindsay's[1] letter comes as a timely reminder that radiation hazards need not outweigh the advantages of cephalopelvimetry, provided that due precautions are taken, and his ingenuity in screening appears to be a worthy safeguard

From an historical standpoint he might have given credit to Chassar Moir[2] (in addition to Blair-Hartley[3]) for emphasising the dangers of the "brim view" in 1956 Indeed, the former should also have special mention for being 10 years ahead of his time in this regard by observing in 1946[4]

> "There is another objection to the use of the standard method (Brim view) the fœtal part occupying the uterine fundus—normally the breech—receives excessively heavy exposure and one which, for all we know, may be harmful to the fœtus"

In congratulating Dr Lindsay I wish that his ingenuity could remedy two further hazards of cephalopelvimetry—namely, reliance upon radiological predictions of the outcome of labour, and the accoucheur who is unable to rely upon his radiological interpretations of cephalopelvimetry

Department of Gynæcology and Obstetrics,
University of Natal, Durban DERK CRICHTON

TOBACCO-SMOKING

SIR,—You clearly disagree (Jan 4, p 32) with my use of intimidation in curing smoking (though you admit that it may be successful) and you regard persuasion as the only permissible psychotherapeutic instrument

I have often presented the case against the smoking of tobacco persuasively and smokers have expressed their agreement about the utter undesirability of smoking in such terms as "I couldn't agree with you more" Yet not long afterwards they have almost invariably lit up! My long experience of curing smoking in fact suggests that in a high proportion of cases persuasion and reason are not enough, because, where his drug is concerned, the addict is not, as a rule, reasonable It is usually necessary to "get at him" emotionally as well as convince him rationally Fear is the great protective emotion and should surely be utilised to protect the individual from lung cancer and other complications of smoking Is it right to withold any highly effective psychotherapeutic agent in the intractible and still increasing disease, tobacco-smoking? Some smokers may resent its use, but some smokers even resent the putting up of non-smoking notices on a minority of railway compartments, judging by the way these are frequently mutilated

My problem is usually one of scaring smokers enough to cure them I scrupulously avoid overstatement except provocatively, when I try to make this obvious Over the past 8 years the public has been given a sporadic series of "inoculations" with inadequate doses of lung-cancer scare The result is that most smokers have acquired such a degree of immunity that they are almost unscareable

Wallasey, Cheshire LENNOX JOHNSTON

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[1] Lindsey, D W *Lancet*, 1957, ii, 1068
[2] Moir, J C *ibid* 1956, ii, 99
[3] Blair Hartley J *ibid* p 46
[4] Moir, J C. *J Obstet Gynæc, Brit Emp* 1946, 53, 492.

SYRINGES CLEAN OR STERILE?

SIR,—Dr Jackson (Jan 18) deserves warm approval for having taken so much thought and trouble about his syringes His hospital also is to be congratulated on its willingness to cooperate with a general practitioner in his attempt to use only sterile syringes in his practice However, when Dr Jackson says that his syringes inside screw-capped metal containers are "autoclaved for me at my local hospital" I hope that he does not mean this literally Syringes in such containers will not be sterilised by autoclaving but only by baking them in a hot-air oven

Department of Bacteriology,
University of Glasgow J W HOWIE

SIR,—The problem of syringe sterilisation in general practice is a difficult one, and there is no doubt that unsterile syringes are frequently used In spite of this, accidents are relatively uncommon

The method of sterilisation mentioned by Dr Jackson in which the syringe is assembled, placed in a screw-capped metal container, and autoclaved, is not really satisfactory The steam may not penetrate into the container and certainly does not reach the plunger of the syringe, the heat is not acting for long enough to penetrate the container and the syringe-barrel, and the plunger is almost certainly not sterilised

Syringes should be sterilised in a hot-air oven in which they are kept at 160° C for 1 hour Alternatively they can be sterilised by infra-red rays, as recently described by Darmady et al[1]

Cuckfield Hospital,
Haywards Heath, Sussex R W P JOHNSON

LONG-TERM TREATMENT WITH ADRENOCORTICAL HORMONES

SIR,—The interesting paper by Dr Davis and Dr Popert in your issue of Jan 4, emphasises the dangers of reducing or stopping cortisone therapy prior to operation Although cortisone and its analogues have been in general use in this country for some years there is still, in the minds of many physicians, practitioners, and surgeons, an insufficient appreciation of the drastic effects which may follow such reduction or cessation Patients who have been on steroid therapy for more than a few days may suffer acute exacerbation of their pre-existing condition when it is stopped and to this may be added symptoms suggestive of adrenocortical exhaustion For some time we have told patients of this danger and warned them against stopping therapy without instructions

Patients on insulin for diabetes mellitus have known for many years the dangers of stopping their treatment in the face of infection or gastrointestinal attacks Nevertheless, they still do so occasionally under the impression that if they are taking no food, no insulin is required, and these are the cases one still sees sent to hospital in diabetic coma or precoma

The rheumatoid arthritic when he experiences an acute gastrointestinal attack also tends to discontinue all treatment until his nausea and vomiting stops and it is again in these cases that we see the cortisone withdrawal syndrome in its most flamboyant form.

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[1] Darmady, E M, Hughes K E A, Tuke, W J *J clin Path* 1957, 10, 291 See *Lancet*, 1957, ii, 1155

In our unit we give written instructions to patients and send a copy to their practitioners emphasising that steroid therapy must not be interrupted and that if the patient cannot take his tablets by mouth during an episode of acute gastric enteritis, cortisone must be given intramuscularly. Should an operation be necessary, dosage of cortisone must be stepped up before, during, and after the operation, for surgical operations are a form of stress and all forms of stress call for increased dosage. We have recently seen cases of peripheral neuritis developing after suddenly stopping steroid therapy and several severe and even fatal cases of withdrawal syndrome are on record as quoted by Dr Davis and Dr Popert.

All this has been well described and emphasised for some years but the fact remains that these points are perhaps not sufficiently widely appreciated even today, and Dr Davis and Dr Popert's article is, therefore, both timely and important.

London, S.W.1 F. DUDLEY HART

MEDICAL PRACTICE IN A CHANGING SOCIETY

SIR,—It is with dismay and despair I read Sir Francis Fraser pontificating in his article in your issue of Jan. 18.

Of course, we would like to have a secretary and a receptionist to do our non-medical work. Of course, we would prefer to improve our standard of care by spending more time on fewer patients. How is this to be done when we are paid seventeen shillings and sixpence a year for our five or six items of service, working out at half a crown or three shillings a time? A plumber who came on a Sunday a few weeks ago, to unblock a drain demanded a pound before starting work—a not unreasonable fee—but let Sir Francis realise, we are valued by the State at no more than one-eighth the worth of a plumber.

It makes us smart to be told that we must try and do better medicine, when we cannot produce a higher standard of care unless we are adequately paid to do so. We have to pay our rent and our children's school fees. The Government has appointed a Royal Commission, and our two-year-old pay claim—the first since 1951—has been ignored. The heartbreaking delay has been perpetuated, and there seems little likelihood of any pay increase and implementation of Sir Francis Fraser's pious suggestions for a decade or more.

London, W.2. P. F. KENNISH

REGULATION OF BODY TEMPERATURE

SIR,—I was interested to learn from the recent contribution of Sir George Pickering (Jan. 4 and 11) that the relatively high temperature of the rectum suggests that it may be a source of heat production by bacterial metabolism in fæces. Some evidence of heat generated from this source has been found in the temperate species of tortoises which are at present being studied.

With low environmental temperatures torpidity is induced which results in hibernation and it is not of uncommon occurrence that specimens with any considerable amount of fæces in the upper part of their rectum will after several weeks of hibernation awaken although the environmental temperature is below that permitting comfortable voluntary activity. On the other hand, specimens which have a comparatively empty rectum do not usually awaken. Presumably the bacterial metabolism which is thermogenic raises the body temperature of small individuals to that required for voluntary activities. We find that with adult specimens with a loaded rectum there is seldom awakening from hibernation, as probably it is a greater task to warm a larger body by this source. This latter observation suggests that awakening from hibernation is not a result of any perineal sensation which induces defæcation.

Unfortunately it has not as yet been possible to record the amount of heat evolved by the fæces while within the body, but it appears that a juvenile specimen hibernating with a loaded rectum will, in a period of between four and seven weeks, at an external environmental temperature of 11°C, have an anal canal temperature 4°C above that of a specimen with an empty rectum. This and related problems are to be investigated.

The rapidly changing immediate environmental conditions within the rectum of any animal, including man, will unfortunately never give a reliable temperature reading for any given period. The belief of Mead and Bonmarito[1] is that the temperature of any region depends on the metabolic activity of the region, the temperature and amount of blood flowing through the region and the gradients of temperature to surrounding regions will never allow the rectal temperature to be as precise as some have in the past thought. This would apply to all parts of the body for there is no organ, tissues, or cells which have the same metabolic activity all the time.

Zoological Society of London,
London, N.W.1 TIMOTHY J. HUNT

SIR,—I read with great interest Sir George Pickering's excellent and thought-provoking articles.

He mentions that "the considerable interval between the entry of endogenous pyrogen into the blood-stream and the onset of fever suggests the formation of a further intermediate substance." "Considerable interval" is rather vague and I wonder what the actual figures were. It is often observed that patients have rigors soon after starting intravenous fluids, in spite of adequate aseptic precautions; this is in all probability an unknown pyrogen reaction. My limited observations of treatment with intravenous T.A.B. vaccine, in gradually increasing doses, suggest that rigors almost always start in 15-30 minutes or not at all. Is this a considerable interval for the formation of an intermediate substance?

Victoria Hospital,
Accrington. S. S. JHAVERI

INFANTILE GASTROENTERITIS

SIR,—Dr. Librach (Jan. 11) appears to have missed the point of our article (Dec. 14). Infantile gastroenteritis due to *Escherichia coli* is a specific disease with known high infectivity. Careful bacteriological examination of the stools to exclude the known pathogenic serotypes of *Esch. coli* in a case of infantile diarrhœa and vomiting is essential before one is entitled to consider the ill-defined field of infantile digestive disorders. Our experience suggests that many cases which on clinical grounds appear to be of the non-infective type actually prove to be mild cases of infective gastroenteritis.

Mild cases of infantile gastroenteritis due to *Esch. coli* treated at home often do well without any antibiotics at all. In hospital the problem is somewhat different and the need for treatment of proved cases falls into three categories:

(*a*) Where the clinical condition warrants it (all severe cases and many of the intermediate group). In severe cases we consider that antibiotic therapy should be started as soon as a stool sample has been obtained, and before the results are available.

(b) Those cases from institutions and nurseries where negative stools are required before discharge.

(*c*) Mild cases from their own homes in order to reduce the chance of cross-infection. It is in this last category that opinions may vary.

Treatment on these lines is surely not "indiscriminate antibiotic therapy."

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[1] Mead, J., Bonmarito, C. L. *J. appl. Physiol.* 1949, 2, 97.

We were surprised that Professor Watkins (Dec 21) is "not impressed with the therapeutic effectiveness of antibiotics", but perhaps he was referring to all grades of severity In severe cases the ease of treatment and the rapid recovery bear no comparison with the difficulties encountered before the advent of antibiotics

Infantile gastroenteritis should be treated on the knowledge of the bacteriological facts and not on clinical impressions It would avoid confusion if this term was used only in those cases in which known serotypes of *Esch coli* were isolated

Hither Green Hospital,
London, S E 13

E H BROWN
E H BAILEY

A FUNCTIONAL NECESSITY

SIR,—Mr Murley's letter in your last issue seems more concerned with attacking the Regional Board and its officers than attempting to deal with the extremely difficult problem of medical staffing in the hospitals As he quotes from correspondence with the Board, your readers will be interested to see, in full, the request which he made for information to be supplied to the Medical Committee This was

1 The numbers of consultants and SHMOs in the various specialties at present working in the region

2 The number of requests for additional consultant staff received from hospital management and/or medical advisory committees since 1948

3 The number of such requests which the Board has been (*a*) able to fill, or (*b*) unable to advertise

4 The number of additional consultant appointments made by the Board without specific request from the periphery

5 The number of requests for additional consultant appointments or additional sessions, emanating from management committees or medical advisory committees which the Board has not agreed to

6 The number of requests for additional consultant appointments, &c, which the Board has not been able to advertise owing to financial stringency (It being presumed that the Board would like to have made these appointments had the money been available)

7 The number of SHMOs who are performing consultant work

8 The number of senior registrars who are "time expired" and seeking consultant appointments

9 Finally, may the medical committee please be supplied with details of any investigations of the medical needs of the region which have been undertaken by representatives of the Board, the Ministry or any other group which has looked into this matter

Mr Murley quotes only an extract from the written reply The reply forwarded to him in fact reads as follows

> "The information requested by him would be most difficult to assemble and would involve a close examination of all the Board's records on medical staffing since 1948—this in itself would be a major undertaking It would then be necessary to analyse them in some detail and the result would still not be satisfactory since in many cases, it would be a matter of opinion as to the net effect of a particular line of action by the Board
>
> "Quite apart from this, the Board's staff is so sorely pressed at the present time, that to embark on this project for Mr Murley would be quite impossible"

This difficult question of the most appropriate medical staffing of the hospitals has been concerning the medical staffing subcommittee of the Board's Establishment Committee for a considerable period of time This subcommittee consists of six members, five of whom are medical

On Oct 16, 1957, the Board sent a deputation to the Ministry of Health asking that most urgent consideration should be given to a number of problems affecting medical staffing, particularly one arising out of the present difficulty over senior registrars, and suggesting a number of solutions The fact that the Ministry of Health have not so far been able to meet the Board in the suggestions which it made, is perhaps due to the intractable nature of the problem as between the Ministry of Health and the profession as a whole

North West Metropolitan Regional
Hospital Board
11a, Portland Place, London, W 1

COTTESLOE
Chairman

MANIPULATION FOR BACKACHE

SIR,—Mr Bremner (Jan 4) defines lumbosacral strain as a chronic localised disc degeneration with associated derangement of the corresponding posterior joints and ligaments from which pain presumably arises, in the early stages it is a subluxation or instability of the posterior joints with associated ligamentous strain and in later stages a true osteoarthritis (Nerve-root involvement and general spondylosis are excluded) The long-term management is arranged as follows

(1) If seriously disabling spinal fusion

(2) *If not seriously disabling*

- (*a*) Reassurance and advice on how "to live with their back", if intelligent
- (*b*) Manipulation for the average hospital patient because he expects something more "positive" than reassurance and advice, and if not given manipulation he will seek it elsewhere

The reasons given for manipulation under (*2b*) have no foundation in pathology and could equally well be put forward as arguments for treating with strapping, plaster, corset, local anæsthetic, cortisone, or even an X-ray! As "a priori" arguments for manipulation, they have no value In addition there is nothing in Mr Bremner's concept of the pathology to justify manipulation If manipulation is to have any objective value as distinct from psychological it must mean either a purposeful and enduring correction of a derangement or the restoration of all or part of a range of movement lost through adhesions It would seem that Mr Bremner realises all this and he attempts to justify the use of manipulation on the purely empirical grounds that it produces "satisfied customers" without having any scientific explanation for this

Given the pathology as described by Mr Bremner I cannot understand how 25 of his 250 cases obtained dramatic relief from (presumably) a single manipulation (unless the result was due to the subsequent physiotherapy) I find it much easier to understand why 61 of his patients found relief only in a lumbosacral corset

I make these observations not in criticism of Mr Bremner's article, since he is assiduously careful to avoid making any claim to diagnose with scientific evidence any derangement of the lumbosacral region which he would profess to be able to purposefully correct by a specially designed manipulative procedure My disagreement is rather with those who advocate a practice which implies such a claim Of this school of thought I would ask

(1) What precisely in anatomical terms do you attempt when you manipulate? It seems to be more generally the hypothesis that there is a derangement rather than adhesions

(2) How do you achieve a precise correction of a unit of the intricate lumbosacral complex by a manœuvre exercised on the exterior of the trunk? I can diagnose with X rays a dislocation of the fifth cervical vertebra on the sixth cervical vertebra and reduce it by a manœuvre based on a knowledge of the method of production of the derangement and check my result by X-ray examination, but I cannot practise in this manner on hypothetical derangements of the lumbosacral-joint complex for which I have no objective evidence

(3) Is it right that throughout the country practitioners should manipulate "slipped discs" if many of them have no personal experience of the nature of a protrusion of the nucleus pulposus as seen at operation? Of some hundreds of disc protrusions I have seen at operation I have never seen one that could be reduced by manipulation Perhaps it is only the

irreversible discs that come to operation What evidence is there for disc protrusions reversible by manipulation? I know of no acceptable scientific evidence for this

War Memorial Hospital,
Scunthorpe
DAVID F THOMAS

SIR,—Mr Bremner is to be congratulated on the successful disposal of a high proportion of chronic-backache patients by manipulation May I, as a general practitioner, who has to live with the "patient who has to live with his back" comment on some aspects of his report

(1) The sole criterion used in this series is the patient's subjective complaint about his back, both before and after treatment There is no indication that information about the person complaining of his back would be of any use here this is the exact antithesis to the modern ideal of treating the patient and not the illness Bomford,[1] in his Bradshaw Lecture of 1952, gave an amusing analysis of his own chronic backache which might aptly be re-read by those who deal with "chronic backs"

(2) The results reported are the immediate (one to two weeks) after-effects of the treatment, surely, in chronic conditions the long-term results are of more interest

(3) It is assumed that, as no attempt is made to "sc manipulation", psychological influence as such is excluded This, however, is doubtful Note how Mr Bremner comments "manipulation is the most convincing" to the patient and if not offered this treatment the patient "may well seek it elsewhere" Treatment, therefore, should be "definitive for this "nuisance disease"

I feel confident that psychologists will recognise in thi type of language familiar patterns of powerful unconscious needs in both patient and therapist General practitioners, too will recognise similarities to their own dealings with assorted chronic complainers In short, it is probable that important psychological factors are at work here and can be ignored only at the risk of a loss of clarity in the results It may well be that the diversity of opinions about so pragmatic a treatment as manipulation is due to disregard of psychological factors

(4) This suggests a possible control experiment in the course of such routine work, by omitting the manipulation in every second anæsthetised patient It would be wise, however, to seek the aid of a psychologist in organising such work

London, W 13
A LASK

CANCER OF THE BLADDER IN CHEMICAL WORKERS

SIR,—We were surprised to read a statement, in the Report for 1956 of the Ministry of Health,[2] on bladder cancers of chemical workers, which we think is misleading without fuller explanation We have drawn attention to this and the department of the Ministry of Health concerned agrees that some clarification is desirable

The statement referred to, about cancers, is

> "Some, such as the scrotal cancers of chimney sweeps and mule-spinners, the bladder cancers of chemical workers and the bone cancers of workers with luminous paints have been so far elucidated that, for practical purposes, they have been prevented and eliminated

A statistical survey,[3] published in 1953, has led to changes in industrial practice that may, if they have been well planned, be expected to diminish the hazard in the future The nature of occupational cancer is, however, such that we should expect many cases to occur during the next 20 years in men who were exposed to risk prior to the changes in industrial practice, even if the precautions taken were completely effective, and very few, or no, cases for about 7 years among men exposed to the new conditions if the precautions are not completely effective The effectiveness of the precautions can, in the long run, only be assessed by a further statistical survey made in about 10 years' time

The Association of British Chemical Manufacturers' report[3] used the following terms " there are now solid grounds for thinking that the practical steps already taken and being taken will successfully overcome the hazard The abandonment of beta-naphthylamine manufacture alone should go an appreciable way to achieve this end The introduction of new plant design and operation together with general improvement in factory hygiene should also greatly increase the margin of safety with the other carcinogens" An incomplete appreciation of the situation thus described may have led the Ministry of Health to indulge in optimistic prolepsis

The possibility of the introduction of new bladder carcinogens into the chemical industry (and other industries) must be borne in mind Already xenylamine (4-amino diphenyl) has produced human bladder cancer in the United States[4]

A search of death certificates relating to workers in chemical occupations where bladder tumour is mentioned amongst the recorded causes of death does not show any falling off in the annual number, 17 being found in 1955 and 16 in 1956 The mean annual numbers for 1945-49 and 1950-54 were, respectively, 13 and 15 These figures do not support the suggestion that "for practical purposes they (bladder cancers in chemical workers) have been prevented and eliminated" (Parenthesis inserted)

Chester Beatty Research Institute,
Institute of Cancer Research,
Royal Cancer Hospital,
London, S W 3
E BOYLAND
R A M CASE

Royal Marsden Hospital,
London S W 3
D M WALLACE

POSTOPERATIVE VENOUS THROMBOSIS

SIR,—I welcome D Rivlin's letter[5] It is sad to read that "it is extremely doubtful whether the incidence of postoperative venous thrombosis is diminishing" That this proves that early ambulation has been a failure would be a very erroneous conclusion The real motive of early ambulation seems to have been grasped by very few people Much thrombosis is of necessity present after operation or childbirth It is the spread of this process into adjoining streams that must be prevented and, unfortunately, most of the conditions favouring this spread are present after operation, foremost among these is the slowing of the blood-stream which allows the platelets to silt out and set into action the process of clotting This blood-clot is inside an undamaged vein, is not firmly adherent, and is easily detached

The rate of flow can be increased by muscular activity and by antigravitational methods Gravity is counteracted by raising the foot of the bed about 9 in , and ankle and knee exercises in bed or walking will increase muscular activity Not all patients are fit to get up soon after a major operation, yet many enthusiasts impose this as a rigid routine For such people, far more benefit would be gained by knee and ankle movements in bed for three minutes in every hour, than by getting them up In fact, the latter can surely be harmful when the patient is frail and in considerable discomfort, and especially so when she has merely been lifted into a chair for some five minutes and then lifted back again As Dr Rivlin says, this is often described as early ambulation There is no ambulation, and in fact the venous return is less efficient than it is in bed with the foot raised I would utter one other word of warning, against the increasingly popular practice of half the ward sitting around the fire together for most of the evening Psychologically, this may be beneficial, but patients allowed the privilege should be warned that it is only on condition that they do frequent knee and ankle exercises

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[1] Bomford, R R *Brit med J* 1953 i 633

[2] Report of the Ministry of Health for the Year ended 31st December 1956 Part II On the State of the Public Health p 103 H M Stationery Office 1957

[3] Association of British Chemical Manufacturers Papilloma of the Bladder in the Chemical Industry London, 1953

[4] Melick W F Escue H M Naryka, J J Mezera, R A Wheeler, E P *J Urol* 1955 74 760

[5] Rivlin S *Lancet* 1957, ii 1290

Thrombotic complications are four times as common in gynæcological operations Surely this is because movements of lower limbs cause much more discomfort after lower abdominal operations and certainly after perineal operations, immobility is the inevitable result

The peak of post-operative thrombosis is at about the tenth to twelfth day, and this coincides with the highest levels of platelet-count, platelet adhesiveness, and plasma prothrombin, a plea is long overdue, therefore, to aid venous return from the legs after operation for at least two weeks This should be achieved by exercises, bed raising, and, of course, early ambulation if the conditions are suitable

London, N W 1 E R REES

OSTEITIS PUBIS

SIR,—I recorded[1] in 1953 that this condition may be found in about 4% of the "rheumatoid" affections of the skeleton, following trauma or sepsis associated with any operations on pelvic structure, and may have more serious extensions than described, for infection of the periosteum may lead not only to the radiographic signs in the symphysis but to signs of ischial bursitis, septic arthritis of the hip, or sacro-iliac joints Though it is often the baffling, painful, and tiresome complication described by your correspondents (Jan 8), it may be painless when first discovered by X-ray examination and may end in fusion at the affected joints, chronic arthritic changes, or, more fortunately, complete resolution

Birmingham JAMES F BRAILSFORD

THE CHECK-VALVE MECHANISM AND THE MEANING OF EMPHYSEMA

SIR,—Consideration of the ætiology of diffuse hypertrophic emphysema has for long been a powerful stimulant to speculation, and the multiplicity of hypotheses emphasises, as a kind of Volker's Law, that we do not know the answer Two types of mechanism may, separately or together, be causative firstly some change in the alveolar wall making it more liable to damage and rupture, and secondly an excessive strain to which "normal" alveoli are subjected and which overinflates and permanently deforms them In his paper in your issue on Jan 11, Dr Lister argues convincingly that diffuse hypertrophic emphysema is usually preceded by bronchitis and bronchospasm There is, however, little experimental evidence to support his conclusion that there is a widespread check-valve mechanism (allowing air to enter pulmonary units but not to leave) and that these units first become overdistended and then emphysematous It is important to state the difficulties in accepting this view

It should first be emphasised that a *uniform* diffuse condition cannot cause overdistension of the airsacs, since the distension must remain within the limits of a person's vital capacity and "healthy alveoli cannot be ruptured by any physiological range of pressure" But if only some pulmonary units have check valves then we have to find a mechanism which will overdistend these but not adjacent alveoli The amount of air entering an airsac will depend mainly on three factors the pressure-drop through the air passage, the resistance to flow through the airway, and the stiffness of the alveoli beyond It is fundamental to the mechanical explanation of emphysema that, in the first instance, the alveoli are of normal stiffness (or compliance, to use current terminology), but even if it is not constricted, a bronchiole or alveolar duct with a check valve will almost certainly have greater resistance to air-flow than a normal bronchiole, unless one regards the valve as similar to a pea in a whistle Furthermore, if the valved unit becomes distended the pressure-drop tending to inflate it will be less than for adjacent unvalved units In other words the "normal" airsacs will be ventilated to a greater extent than the valved ones, which can only be inflated to the maximum static elastic pressure of the lungs which we know they can withstand without rupture

Dr Lister thinks it more likely, however, that the valved units are overinflated by positive pressure within the large airpassages in coughing, "as in pumping up a tyre" But the intrapulmonary pressure must rise with the intratracheal pressure in the expiratory phase of coughing, so that there is no pressure-drop to pump air into the alveoli Even were there such a force it would tend to overinflate "normal" units rather than valved ones, for the reasons given above Furthermore, if the entire contents of the air-passages (150 ml) could in some way be pushed into the alveoli (2500 ml) this would cause little extra distension

There are three possibilities which might resolve the problem

(1) If in the initial changes in diffuse hypertrophic emphysema some alveoli are so damaged as to be less stiff (more compliant) than others, these would then tend to overinflate, the mechanical factors would then be secondary to earlier structural changes, and it is not necessary to incriminate check valves to explain progress of the disease

(2) If units containing check valves have a lower resistance to air entry than "normal" units It is difficult to conceive such a mechanism, and if, as one suspects, the contrary is true the mechanical forces described above would tend to distend "normal" alveoli rather than valved ones

(3) If the alveolar walls are damaged by maintained pressures which do not cause harm when applied transiently in normal breathing Such pressures might be found beyond check valves in the early stages of emphysema

These are theoretical considerations, but the possibilities described above should be susceptible to experimental test In the meantime, the evidence for a check-valve mechanism in the early stages of diffuse hypertrophic emphysema is very largely based on speculation, and it is important to emphasise the difficulties inherent in this theory

Department of Physiology,
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G C R MORRIS
J G WIDDICOMBE

INCIDENTAL DANGERS OF X-RAY THERAPY

SIR,—Not only the electrocardiographic changes mentioned in your leading article of Jan 4 but also actual cardiac infarction may follow therapeutic irradiation of the thorax Although the myocardium resembles skeletal muscle in its resistance to X-ray damage small and medium arteries are sensitive and can become occluded by the intimal proliferation described by Tricot et al[1] or perhaps by a similar fibrinoid necrosis to that observed by Professor Wilson and his colleagues (Jan 4), in the kidney

In two cases under my observation extensive infarction occurred six months after irradiation[2] The attacks were of great severity, accompanied by disturbances of conduction, and were followed by a degree of clinical and electrocardiographic recovery that one could not expect after atheromatous occlusion Both patients were women under 50 who had had no previous angina

The long interval is interesting in the light of Professor Wilson's finding of delayed structural changes in the kidney and corresponds with that elapsing before the post-radiation mediastino-cardiac reaction of Blemenfeld and Thomas [3] and Rose and Wolferth [4] It may well obscure a relationship that is commoner than either radiotherapists or " the neighbours " realise

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[1] Brailsford, J F Radiology of Bones and Joints London, 1953

[1] Tricot, R, Baillet, J, Helmke, G *Arch Mal Cœur*, 1954, 47, 922

[2] Pearson, H E S *Proc R Soc Med*, 1957, 50, 516

Whittington Hospital,
London, N 19

H E S PEARSON

INTRATHECAL PHENOL FOR INTRACTABLE PAIN

SIR,—The report by Dr Nathan and Dr Scott in your issue of Jan 11 corresponds closely with the results obtained during the past year in Edinburgh using a 7½% phenol-'Myodil' solution

As with their material, necropsy has revealed no changes in the spinal cord, its coverings, or nerve-roots which could be attributed specifically to the effect of the injected material

However, 4 patients had their spinal cords exposed at the site of injection within two to four weeks of the injection and each showed a marked localised arachnoiditis Over a distance of about two inches the arachnoid was quite opaque and pink and adherent to the dura and underlying structures, making exposure of the spinal cord tedious

So far, no patient subjected to this form of treatment has developed signs suggestive of a progressive adhesive or obliterative arachnoiditis following the injection, but until a sufficient period of observation has been completed it would seem to be prudent to restrict the intrathecal use of carbolic acid dissolved in myodil to the relief of pain of malignant disease

Department of Surgical Neurology,
Royal Infirmary, Edinburgh

ALLAN S BROWN

A PLASTIC APPROACH TO SURGERY

SIR,—It is surprising that Mr Heanley (Jan 11) as a plastic surgeon should advocate the making of incisions in the direction of Langer's lines, for in the face, where the best cosmetic result is particularly desirable, the line of election for a scar bears no relation to Langer's lines

As Le Gros Clark [5] has pointed out

> " with the movements of facial expression, flexure lines appear momentarily in the skin at right angles to the pull of the fibres of cutaneous muscles In other words, their pattern is determined by the arrangement of the underlying musculature With advancing age, as the result of the progressive loss of the elasticity of the skin, these creases become established as permanent wrinkles "

The illustrations of Kraisse [6] have shown convincingly that at many points the direction of the lines of election and that of Langer's lines are at complete variance and it would appear that when they do coincide this is quite fortuitous

The continued lip-service paid to Langer's lines in most surgical textbooks would suggest that these facts are not widely enough appreciated

Royal Infirmary,
Glasgow

IAN A MCGREGOR

CHRISTMAS QUIZ

DR N HOWARD-JONES writes

"Supplementing Dr Gurney Smith's correction (Jan 4, p 58) to the excellent Christmas Quiz provided by Dr Ffrangcon Roberts, I would point out that the *St Bartholomew's Hospital Reports* of (as far as I recollect) the 1870s contain a most amusing article by Robert Bridges on the casualty department of his hospital The answers to the quiz contain another slip 'Jesuits' bark' was not quinine, but the bark from which quinine and other cinchona alkaloids were subsequently isolated "

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[3] Blemenfeld H Thomas S F *Radiology* 1945 44 335
[4] Rose, E Wolferth C C *J Amer med Ass* 1941 116, 2649
[5] Le Gros Clark, W E The Tissues of the Body p 277 Oxford, 1945
[6] Krausse C J, *Plast reconstr Surg* 1951, 8, 1

Obituary

JAMES COUPER BRASH

M C, M A, M B Edin, M D Birm, LL D St And, D Sc Leeds,
F R C S E

Emeritus Professor Brash died at his home in Edinburgh on Jan 19, at the age of 71 He was one of the great figures and personalities in British anatomy, and his death will cause many practitioners of medicine the world over to feel a deep sense of personal loss

He was born in Helensburgh, and was educated at George Watson's College and Edinburgh University where he entered on an arts course The knowledge of literature, philosophy, and Latin that he then gained formed the basis for his own philosophy of life He recommended others to cultivate, as he himself certainly did, the tranquil mind, the quality of imperturbability and calmness in times of emergency These indeed formed the theme of his promoter's address to the new graduates in medicine in Edinburgh in 1940

After graduating M A, Brash entered on a combined science and medical course in which he distinguished himself in many subjects and extracurricular activities He was prominent in several student societies and became senior president of the Students' Representative Council After graduating M B in 1910 he became house-physician in Edinburgh Royal Infirmary to the late Sir Thomas Fraser In 1911 he joined the anatomy department of Edinburgh University as a demonstrator under the late Prof D J Cunningham—and this connection was always a matter of pride to him From Edinburgh he moved to the anatomy department at Leeds, but in 1914 he joined the R A M C, and while with it served in France and Belgium, attained the rank of major, and was awarded the M C Returning to academic life he was later translated to Birmingham, where he became professor of anatomy and dean of the faculty of medicine He was responsible for the planning of many of the developments that led to the formation of the new Medical School in Birmingham, and for such responsibility he was eminently well qualified He succeeded Prof Arthur Robinson in the chair of anatomy at Edinburgh University in 1931, and for 23 years he laboured ungrudgingly and without stint for his alma mater His lectures were always most carefully prepared expositions of the subject with which he was dealing, and on occasions he was carried away by his own enthusiasm He and the late Dr E B Jamieson established a close and firm friendship that matured over the years, and they were co-editors of the 7th and 8th editions of *Cunningham's Text-book of Anatomy* and also were co-editors of two editions of *Cunningham's Manual of Practical Anatomy* The last editions of the manual were, however, entirely Brash's work, and he was also sole editor of the most recent edition of the textbook

His main scientific interest was the development and growth of bone, and his Struthers lecture on the subject in 1933 to the Royal College of Surgeons of Edinburgh is now regarded as a classical study Much of his original work was associated with the growth of the jaws and palate, and he had a particular interest in the ætiology of irregularity and malocclusion of the teeth The mechanism involved in the movement of the teeth during growth of the jaws always fascinated him and his madder preparations threw great light on the subject His eminence as an anatomist was recognised by the Anatomical Society when he was elected president for 1945–47 and also by the Universities of St Andrews and Leeds from which he received honorary degrees His anatomical skill was brought to the notice of the general public through his researches and meticulous work in connection with the

Ruxton murder case, and he and Prof John Glaister published a volume in 1937 dealing with the medicolegal and other scientific aspects of this case In 1955 he published an important text on the neurovascular hila of limb muscles

R W, an Edinburgh colleague who migrated across the Firth of Forth, writes

Professor Brash's interests were multiple and on golf course and in trout stream he showed the same enthusiasm as at work in his laboratory His sense of pawky humour was a feature of his lectures and after-dinner speeches and through it he relieved the tenseness of many an examination He was a man who always gave more than he received and in doing so gave himself great pleasure, students without number and graduates sought his counsel and advice knowing that in doing this they would receive an opinion that would be in their best interests For over 45 years he owed much to Mrs Brash and through her he came to have a deep love for St Andrews and its University

THOMAS KIRKPATRICK MONRO

M A, M D Glasg, F R F P S

Dr T K Monro, emeritus regius professor of the practice of medicine in the University of Glasgow, who died on Jan 10 at the age of 92, had won an honoured place in Glasgow by the kindliness and skill with which he served the city's patients and the learning and humanity which he offered the students in the city's medical schools His interests as a physician and a bibliophile were happily joined in his famous collection of editions of *Religio Medici*

He was born at Arbroath, where his father, Dr William Monro, was in practice After graduating M B from the University of Glasgow in 1888 he continued his medical studies in Vienna, Berlin, and Paris Soon after his return to Scotland he became pathologist to the Victoria Infirmary in Glasgow He had held the chair of medicine at St Mungo's College and a clinical lectureship at the Royal Infirmary for over ten years when in 1913 he was appointed to the regius chair at the University

His writings on his own subject included his *Manual of Medicine*, his *History of the Chronic Degenerative Diseases of the Central Nervous System*, and a monograph on Raynaud's Disease His book on the *Physician as Man of Letters, Science, and Action* happily presented his profession to a wider circle of readers He retired from his chair in 1936, and the following year the University of Glasgow conferred on him the degree of LL D Two years later the Royal Faculty of Physicians and Surgeons elected him to their honorary fellowship, an unusual distinction for one who had already served as their president

The following tribute is taken from the address which S A gave at Professor Monro's funeral on Jan 14

Thomas Kirkpatrick Munro found his life work and his inspiration in the day-to-day care of sick people in the hospitals and homes of this city A supreme master of the art of clinical practice, he enhanced the value of his skill by kindness born of compassion, and his whimsical sense of humour endeared him to his patients and to his students He was an outstanding teacher—especially for those students sensitive to the great adventure opening before them in this realm where science merges into art Acutely aware of the needs of the individual patient before him, it was nevertheless by a light more remote yet more vivid that he saw the detail of his task

His skill and shrewdness and humanity at the bedside were the blossom of a fine intellect nurtured in the climate of true learning he read his classics in the original and refreshed his mind with music, history, and mathematics, and in the twilight of his later years, though frail and blind, by the sense of touch he lived among his favourite authors and walked with greatness He loved the open country, the wind and the rain, and while walking and angling he cherised the boon of solitude Topics which might seem remote from the mind of a scholarly physician came within the ambit of his encyclopædic knowledge he could startle the expert by dissertations on locomotive construction, and others he would entrance by his devotion to the circus It would be a fitting tribute to his diverse accomplishments if they were to be recorded in his own book—*The Physician as Man of Letters, Science and Action*—for in these pages he reveals his affinity for the man of many parts So notable and ardent à bibliophile inevitably grows into his books The pages of the *Religio Medici* and *Christian Morals* were so close to Thomas Monro that he seemed to breathe the same air as Sir Thomas Browne, and with him might well have said—

> Some things are dictated for our instruction and some
> acted for our imitation
> He honours God, who imitates him, for what we
> virtuously imitate we approve and admire

CHIRANJI LAI PASRICHA

M A, M B Cantab

Lieut -Colonel Pasricha, who died in London on Jan 11, was a former director of the School of Tropical Medicine at Calcutta From 1948 to 1955 he was medical adviser to the High Commissioner at India House, and he was often to be seen at scientific and social gatherings of doctors in London

He was born in the Punjab, and educated at Leys School and Caius College, Cambridge, where he took a first in the natural sciences tripos He qualified in 1920 from St Bartholomew's Hospital, where he won the Shuter scholarship Soon afterwards he passed into the Indian Medical Service and later saw service in China as well as in India In 1933 he became professor of pathology and bacteriology at the Calcutta school In 1939 he was awarded the Minto medal for medical research His work included investigations into the treatment of cholera with the newer sulphonamides, and on choleraphage, snake venoms, epidemic dropsy, and sprue He succeeded the late L E Napier as director of the school in 1945, and he also was superintendent of the Carmichael Hospital for Tropical Diseases in Calcutta During the late war, he was A D M S at Army Headquarters, New Delhi, and at this time he largely rewrote the *Field Service Hygiene Handbook* (1945)

In 1948 he came to London as medical adviser to the High Commissioner for India P H M-B writes

Pasricha was an admirable public-relations officer by reason of his friendliness, his accessibility, and his attraction to the British way of life, and adherence to its ideals as well as to those of Indian culture It was always an experience to get into touch with him and thereby to imbibe some of his vigour and enthusiasm At medical meetings his tall, erect military figure was welcome, and the benignant smile which lit up his face was indicative of the character of this popular man He always remained a loyal friend of this country, a devoted and loyal son of Cambridge, and proud of his associations with St Bartholomew's

Appointments

CRAIGHEAD, ISOBEL B, M B Edin, D P H assistant M O (child welfare), Edinburgh

Colonial Appointments

BOYD, P R W, M B Lond M O grade B (institutions), Trinidad
DASENT, L E., M B N U I, D T M & H M O grade B (institutions), Trinidad
GEHR, A E M D Hamburg M O, leprosy service, Eastern Nigeria
HOGERZEIL, L, M O, leprosy service, Eastern Nigeria
PYDIAH, S R, M B Madras M O Mauritius
ROBERTSON M J, M R C S, D T M & H M O, Hong Kong
RUSH, S V, M R C S, D O M S senior specialist, Federation of Nigeria
WARD, J R, L.R.C.P E. M O, Kenya

Notes and News

ONCHOCERCIASIS

AT a meeting of the Royal Society of Tropical Medicine and Hygiene in London on Jan 16, Dr A R D **ADAMS** (Liverpool) opened a symposium on onchocerciasis with a short general account of the disease adding that he had seen only one instance of serious eye lesions in his considerable series of European cases

Prof A W **WOODRUFF** commented on the rarity of ocular lesions in Africans examined in Calabar, where almost all were infected with the disease On the other hand eye lesions—mostly slight—were found in 12 out of 76 patients (72 Europeans) seen in London Eye lesions might therefore be present in light infections and absent in heavy infections possibly the high gamma-globulin content of the sera of Africans, so constantly exposed to multiple infections, provided a protection. It seemed that some other factor was needed to produce blindness Onchocerciasis might be suspected . there was unexplained pruritus, rash, eosinophilia, or eye disease in persons from the endemic areas, and filarial complement-fixation test and skin tests were useful Diethylcarbamazine would kill not only the microfilariæ but also the adult worms, if enough was given This was disputed by Dr F **HAWKING**, who, though acknowledging the drug's great value against microfilariæ, did not find it lethal to the adult worms For this suramin was necessary

The strongest critic of the blindness concept was Mr D P **CHOYCE**, who showed slides illustrating those lesions of the anterior segment of the eye which are admittedly due to onchocerciasis—keratitis commonly, iritis more rarely—but which in the Cameroons did not often lead to more than slight interference with vision He did not think that this infection could cause cataract The lesions of the posterior segment which caused blindness and which had been attributed to onchocerciasis—optic atrophy, retinal degeneration—were, he thought, probably of different ætiology, and there was no good evidence that they were onchocercal Optic atrophy was caused by vitamin deficiencies, syphilis, and other conditions common in Africa, and the form of choroidoretinal degeneration seen there was remarkably similar to the hereditary diseases known in Britain and transmitted as a genetic dominant Moreover, as microfilariæ of *Onchocerca volvulus* were not found in the blood-stream, it was difficult to understand how they could gain access to the optic nerves and choroid Mr Choyce concluded therefore that onchocerciasis was probably not a serious cause of blindness, though he admitted that it might have an adverse effect in trachoma, leprosy, and other affections of the eye

Dr W E **KERSHAW** (Liverpool) agreed with this general conclusion, on epidemiological grounds after investigations in the Cameroons The anterior eye lesions were related to the intensity of infection but were not blinding lesions, but the incidence of posterior eye lesions, the blinding lesions, bore no relation to intensity of infection Dr R S **BRAY** reported work done in Liberia in which no blindness was found in a group of African onchocerciasis patients in whom there was much deficiency disease

These arguments were not enough to shake the belief of several speakers who had lived in the onchocerciasis areas of West Africa Dr B B **WADDY** thought that heavy infections in childhood might lead to blindness in later life, and that onchocerciasis could cause cataract Optic atrophy might possibly be related to extensive use of tryparsamide for sleeping-sickness Lieut-Colonel J H **WALTERS** recalled the high incidence of posterior eye lesions in peoples living near rivers, who left those parts on that account Optic atrophy certainly might be due to syphilis, but that was commoner in towns than in rural areas such as those in which onchocerciasis flourished Dr J L **MCLETCHIE** pointed out that blindness was common in Northern Nigerian onchocerciasis areas, which were in a dry climate, but rare in the south where the climate was more moist.

Dr A B **RAPER** showed photographs of a condition of dwarfism, in children in the onchocerciasis areas of East Africa, which had very characteristic features—muscular wasting, stunting of growth, kyphosis, and a characteristic facial profile All the patients were heavily infected with onchocerciasis

PATIENTS' PARLIAMENT

UNDER what he calls the " grandiloquent " title of " creative group therapy " Dr George Day describes [1] efforts at self-help by the patients at a private sanatorium in Norfolk Irritated by high prices in local shops, some of the patients opened one of their own, and, having no overheads, it prospered Each corridor supplied a voluntary shopper—one of the ambulant patients—who ran errands for bedridden neighbours One such volunteer from each corridor took a seat in the " Patients' Parliament ", which met weekly and in the course of some ten years spent the shop's profits on books, games, records, broadcasting equipment, a television set, a film-projector, a gramophone, a typewriter, and such useful items as irons and hairdryers Less to raise funds than to give everyone a feeling of participation, half-a-crown a month was levied on all patients who could conveniently afford it

Early in its career the Parliament, which was not elected but self-perpetuating by cooption, began to hear and discuss patients' complaints and suggestions Dr Day acted as Speaker—literally, for he could speak but not vote He had a veto on medical grounds, and at first put right proved complaints, later these tended to be solved by the patients A new patient would find himself visited by ambulant ones as a routine—to see whether he wanted anything, not to gossip—and very quickly felt at home Thus the spirits of self-help and of help-your-neighbour were fostered, and morale was high

MEDICAL FILM

A NEW film, *Ergot—The Story of a Parasitic Fungus* (16 mm , sound, colour, 26 minutes, Britain 1958), traces briefly the discovery and therapeutic use of ergotamine and ergometrine

The film opens with numerous references to ergot poisoning from the 16th century onwards Half the film is then devoted to the life-cycle of the parasite and methods of growing it under controlled conditions for medicinal purposes The symptoms of migraine are set out, and reference is made to a preparation of ergotamine tartrate including drugs to counter its side-effects Prof Chassar Moir describes the discovery of ergometrine in 1935, and finally a patient being delivered in the maternity department at University College Hospital, London, is seen to be given an intravenous injection of the drug

This is a good film, particularly interesting in the sequences on the history of ergot poisoning and on the cultivation of the parasite Douglas Fisher s colour photography is superb, and the commentary is informative

Copies may be obtained free of charge from the Wellcome Film Library, 183, Euston Road, London, N W 1

University of Cambridge

On Dec 21 the degree of B Chir was conferred on the following

R. A Aiken G M D Archer, A M Barnie-Adshead, D G Beynon, W A Brighouse, J H D Briscoe, Andrew Brockman Margaret Bulmer, I E. Bush A J Cameron, L. J Chalstrey, Susan J de Graaff Hunter, A. J Dell, R. C Dobbie P M E Drury, Christopher Dulake, A. J Dyer, Nigel Edwards R H Ellis, R. A Elson N J B Evans, P W Fisher, A F Fleming, David Freeman, C. S Goodwin N J C. Grant P C. Green, P R. Greenfield A H Henderson, N E S Holden, H C Hollingworth, A W Jowett, B S Kerrett, Susan A Leaver A C W Lewis, A D MacAdam Napier Malcolm P M S Margand, B S Mather, John Miller, J G Miller, A B J Miller-Williams, E. W R. Oakden, Miles Parkes, D J S Pendlebury, Neil Powers, P H Rack, R. S O Rees, M B Rees-Jones, M W Riddall D J Riley, Julian Rivers-Kirby, P D Rohde, G I Sinclair David Tidmarsh J C. Twomey, Peter Weston M C. Woodhouse F C Worlock.

University of St Andrew

On Jan 10 the following degrees were conferred

M.D—F W Wigzell

Ph.D—P R. Roy

M.B, *Ch.B*—J C. Anderson Margaret M Arrowsmith, Campbell Calder Marie M Deacon, S A Khalq, A M C. Macgregor, G J Robertson P C. Robson L. W J Ross, I M Stewart.

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1 Day G [illegible] *Med.* 1957 1, 119

University of London

On Dec 11 the degree of PH D in the faculty of medicine was conferred on J G Howard

University of Liverpool

A symposium on the frontal lobes, organised by the department of studies in psychological medicine, will be held on Saturday, March 22

The speakers will be Dr Italo Calma, Dr Hugh Jarvie, and Mr Walpole Lewin Further particulars may be had from Dr Jarvie, 77, Bedford Street South, Liverpool, 7

University of Glasgow

On Jan 11 the following degrees were conferred

M D—J B Brennan, R W Bryson, E C Easson, *Kenneth Fraser, A W Gardner, *I S MacDonald, R L Orchardson, *W O Thomson

* With commendation

Ph D—J K Burns

M B , Ch.B—Nasiru-Deen Akilade, A W Baird, I W MacA Baxter, J S Begg, W D S Blaikie, J S Carlisle, Andrew Craig, T W Cross, P J Docherty, J R Donaldson, William Ducat, J P Duffy, R L Elder, Christina C Hall, Philomena C Hynes, R G S Leask, J R Logan, A W Macara, J R L McConnell, H N Macdonald, A J Mackintosh, I C D Martin, A C Miller, I R Pendrigh, Susan M Ritchie, C A Robertson, A R Sarbah-Yalley, C J Schwarz, Gwen J Scott, J D Simpson, Samsoondur Sonah, L G Stewart, Margaret G Wallace, A F Wright

Royal Microscopical Society

Mr John Bunyan, L D S , Leverhulme research fellow at St. Mary's Hospital Medical School, has been elected president of the society

The Guild of Teachers of Backward Children

This guild will hold its second national conference at Goldsmith's College, London, on April 18 and 19 The hon secretary of the guild is Mr S S Segal, 10, Fielding House, Boundary Road, N W 8

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold a public hearing on Friday, Jan 31, at Church House, Great Smith Street, London, S W 1, at 11 15 a m Representatives of the Royal College of Physicians of London have been invited to attend

Training Posts in Hospital Administration

Applications for a further 16 training posts for prospective hospital administrators are invited

The posts are open both to young officers already employed in the National Health Service and to graduates and professionally qualified people who wish to make hospital administration their career Further particulars may be had from the Ministry of Health, Savile Row, London, W 1

College of General Practitioners

Butterworth gold medal—The subject for this year's prize essay, by a member or associate of the college, is Second Opinions Further particulars may be had from the chairman of the awards committee of the college, 41, Cadogan Gardens, Sloane Square, London, S W 3 Essays must be submitted not later than Sept 20

Royal Air Force Appointments

Air Commodore G A M Knight has been appointed deputy director-general of medical services in the Royal Air Force with the acting rank of air vice-marshal, in succession to Air Vice-Marshal L M Corbet who is retiring Group-Captain J F Dales has been appointed principal medical officer, 2nd Allied Tactical Air Force, with the acting rank of air commodore

Confederation of Health Service Employees

At a conference of the confederation held in London on Jan 15 delegates rejected a proposal to impose a national ban on overtime for all members (*Times*, Jan 16) Since September temporary bans on overtime have been imposed on mental hospitals in different parts of the country, and the results of these local bans were criticised at the meeting Some speakers doubted whether a ban on overtime would now be an effective way of showing members' discontent A delegate said that, owing to a change in conditions of the labour market, hospitals at Lincoln, and he believed elsewhere, now had more staff than at any time in the past six years

World Health Organisation

The Republic of Czechoslovakia has resumed active participation in the work of the World Health Organisation Czechoslovakia became a member State of W H O in 1948, but in 1950 discontinued active participation During 1957 Albania, Bulgaria, Poland, the U S S R and Rumania announced their resumption of active participation in W H O Member States which still remain inactive are Hungary, Ukranian S S R , and Byelorussian S S R

Executive Board—The twenty-first session of the Board began in Geneva on Jan 14, under the chairmanship of Sir John Charles The chief item on the agenda is the examination of the Director-General's proposals for programme and budget for 1959 Emergency supplies of vaccine were approved for Ceylon, where floods have covered a third of the island's surface, 300,000 people are estimated to be homeless, and epidemics of typhoid and cholera are feared Half a ton has already been sent, and another quarter of a ton will soon follow Part of the cost will be reimbursed by Ceylon

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CORRIGENDA *Phæochromocytoma of the Urinary Bladder*—In the article by Dr B R B Lumb and Dr G A Gresham (Jan 11, p 81) the year in the first line of the fourth paragraph of the case-report should have been given as 1956 In the fourth line of that paragraph and in the penultimate line of the sixth paragraph the noradrenaline level was in microgrammes In fig 2 the specimen was reproduced at less than actual size

The Check-valve Mechanism and the Meaning of Emphysema—In Dr W A Lister's article (Jan 11, p 66) the illustration shown as fig 2 was in fact fig 1, and that shown as fig 1 was fig 2

Diary of the Week

JAN 26 TO FEB 1

Monday, 27th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr John Marshall Observations on Spontaneous and Induced Paræsthesiæ in the Upper Limbs
MANCHESTER MEDICAL SOCIETY (Medical School, University of Manchester)
9 P M *General Practice* Dr Aron Holzel Allergies in Children.

Tuesday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Dr D H M Woolam Experimental Approach to the Problem of Congenital Malformations (Arris and Gale lecture)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr William Sargant, Dr Richard Asher, Prof E J Wayne Sedation and Stimulation of Man
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr J A Fraser Roberts Blood-Group Genetics
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Sir George Pickering Hypertension in Pregnancy
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr G C Wells Cutaneous Sarcoidosis
ROYAL STATISTICAL SOCIETY
5 30 P M (Westminster Medical School, Horseferry Road, S W 1) Dr D D Reid *Mortality of Miners*

Wednesday, 29th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Prof Arnold Sorsby Experimental Degeneration of the Retina
POSTGRADUATE MEDICAL SCHOOL
2 P M Prof L J Witts Aspects of Iron Deficiency
INSTITUTE OF DERMATOLOGY
5 30 P M *Dr Henry Haber Hamartomata*
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr Ian Longmuir Aspects of Tissue Respiration
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St Vincent Street, Glasgow
5 P M Sir Roy Cameron Problem of Biliary Cirrhosis

Thursday, 30th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr G F Murnaghan The Mechanism of Congenital Hydronephrosis (Hunterian lecture)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P.M (London School of Hygiene and Tropical Medicine) Dr Edith Bülbring Physiology and Pharmacology of Intestinal Smooth Muscle
INSTITUTE OF DERMATOLOGY
5 30 P M Dr C D Calnan *Drug Allergy*
ROYAL STATISTICAL SOCIETY
7 P M (Leicester College of Technology, The Newarke, Leicester) Dr W R S Doll Smoking and Cancer of the Lung
UNIVERSITY OF ST ANDREWS Queen's College, Dundee
5 P M Sir Roy Cameron Chemical Mediation of Inflammation

Friday, 31st

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr Cecil Flemming Observations on Secondary Carcinoma in Bone
4 P M Dr K W Donald Hæmodynamic Changes in Mitral Stenosis and the Findings after Operation

The Lancet · Saturday 1 February 1958

BETWEEN GUESSWORK AND CERTAINTY IN PSYCHIATRY*

AUBREY LEWIS
M D Adelaide, F R.C.P
PROFESSOR OF PSYCHIATRY, UNIVERSITY OF LONDON

(concluded from p 175)

An effect of growing, but excessive, confidence in the power of psychiatric treatment is discernible in the changing attitude towards those who are delinquent or may become so The recent Royal Commissioners on the Law relating to Mental Illness and Mental Deficiency assumed that doctors can tell which persons of psychopathic personality will benefit by treatment, and what treatment will be needed, consequently they recommend that compulsory powers to force a psychopathic patient into hospital should be used only when it is "clearly established" that he needs a particular form of treatment, which the hospital in question can provide, they recommend more extensive compulsory powers over adolescents and young adults who show psychopathic personality, because "it is generally agreed that treatment or training is most likely to be successful if it can be given at this stage" It may well be that both these assumptions about the benefits of treatment for psychopaths will turn out to be warranted but as yet they rest on the certainties or the clinical impressions of those who took part in the treatment and on unchecked appraisal of the association between outcome and treatment No controlled studies, of adequate size, have been carried out, and many of the difficulties which have so far precluded this were demonstrated in the investigation of a cognate problem—whether juvenile delinquents and "pre-delinquents" benefit from having a kindly older person to whom they can turn for friendship and guidance Richard Cabot had supposed they would, an elaborate inquiry, with well-matched controls, was carried out to test his hope This investigation had nothing to do with psychiatric treatment, nor were psychiatrists concerned in the analysis of its findings, but it afforded a model of honest, hypothesis-testing, longitudinal study of the effects of deliberate intervention It exposed weaknesses in design and execution which can be foreseen now and guarded against, it demonstrated that social investigations concerned with human beings over a period of years cannot be carried out wholly according to plan, yet can be made to answer a correctly stated question, and it threw light on our ability to predict behaviour. Prognosis is more difficult in psychiatry than in other branches of medicine, as Kraepelin insisted some psychiatrists, it is true, pride themselves on their gifts in this direction, but their complacency usually has weak foundations Criminologists have been in the same boat

In the Cambridge-Somerville study just referred to, three experts in criminology (one of them a psychiatrist) predicted what would be the later social adjustment of the 782 "difficult" or "pre-delinquent" boys, aged about 9 years, who were reviewed for the study, a similar prediction was made by the children's teachers, and it emerged that there was a correlation coefficient of 0 48 between the actual outcome on the one hand and the predictions both of the experts and of the teachers on the other In other words, the predictions were above what would occur by chance, but experts in juvenile delinquency were no better at predicting what would happen to these children than were their school teachers Moreover, both the teachers and the experts predicted more delinquency than actually occurred, so if there had been no "untreated" group for comparison they might have inferred—mistakenly—at the end of the investigation that the discrepancy between their predictions and the actual outcome was attributable to the benefits of the "counsellor" scheme of treament provided (Powers and Witmer 1951)

The most recent and sophisticated prediction study is Mannheim and Wilkins's inquiry into the effects of borstal training Besides constructing prediction tables which they validated, they found it expedient, like others before them, to provide individual case-studies—i e, to combine the clinical with the statistical method, in order to "demonstrate the variety of factors which, combined, may produce the same statistical score, to work out a typology of cases related to the various score classes, and to make a special study of atypical cases, i e, cases who, in spite of favourable statistical scores, actually become failures, and vice versa" In their view the control technique, though in many ways indispensable, is insufficient as the only method of evaluating the diverse patterns and changes in the behaviour of individuals (Mannheim and Wilkins 1955) But Mannheim, in expressing this view apropos of the Cambridge-Somerville study, concluded that such investigations will have to be "in keeping with the experiences of experimental social science rather than those of medicine" (Mannheim 1953)

This seems an innocuous conclusion But it contains the chief elements of a vital controversy Psychiatry is, like criminology, a form of applied social science it is also a branch of medicine If there is an intrinsic opposition or sharp difference, as Mannheim implies, between the methods appropriate to study of social experiments and those of medicine, psychiatry will be pulled hither and thither, in a bewildering zigzag I do not believe there is such an opposition, but the literature might suggest it—and the progress of psychiatry does look a little indecisive and wobbly at times The problem is to be found in the uniqueness, the singularity of each individual

In the practice of psychiatry, attention must be concentrated on the individual Because he is unique and extremely complicated, he does not seem wholly catchable within a scientific net The succession of events which pertain to the medical, as to the social or psychological, course of an individual's life can, it is true, be predicted to some extent, and designedly influenced, by applying general principles to the historical and observational data we have about him but there is still something over, consequently intuitive processes often play a large part in determining the physician's prognosis and treatment—especially in psychiatry The doctor's procedure may hardly include at all the strict deductive application of a general theory to a particular, narrowly stated case, and it differs manifestly from that of the experimental biologist who does his utmost to get rid of uniqueness in his experimental animals This difference applies to the practice of psychiatry But it does not apply to the psychiatric investigator who must concern himself with what is common to human beings, or to classes and subgroups of human beings

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* The Bradshaw lecture for 1957, delivered before the Royal College of Physicians on Nov 7

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The controversy is not between medicine and the social sciences, or between medicine and the biological sciences, but between two schools of thought within the social sciences Their debate has enlisted some notable disputants There is guerilla warfare between the adherents of the "nomothetic" school, which seeks general laws and employs the procedures of the exact sciences, and the "idiographic" school, which endeavours to understand some particular event Both approaches, as Gordon Allport has urged, have value in studying personality But the proportion of idiographic to nomothetic study can be excessive and there can be little question that this has been the case in psychiatry Hence its weakness on the very ground where idiographic study should be most potent—the understanding of individuals to such a degree that their behaviour can be predicted

Meehl, in a thoughtful monograph on this matter, collected all the published instances in which predictions arrived at by the skilled judgment of a clinician were compared, as to their correctness, with those arrived at mechanically by someone who had not seen the patients but who made appropriate calculations In all but one of the twenty studies examined, the actuarial or cookery-book approach yielded results as good as those of the clinician, or better (Meehl 1954) It would be imprudent to draw from this the conclusion that clinical prognosis is a superfluous exercise, and that prediction had better be handed over to the clerks and computors impartial judges like Vernon have pointed out that the clinical method—and in particular the clinical interview—has advantages which the actuarial method, based on psychological tests and biographical items, does not possess

Informative as the idiographic approach has proved, and fertile as it will doubtless continue to be, it contains no built-in safeguard against persistent error Such safeguards are essential, for, as Karl Popper puts it, "if scientific objectivity were founded upon the individual scientist's impartiality or objectivity, then we should have to say goodbye to it" Yet the safeguards contained in the scientific method are repugnant to some who devote themselves to psychotherapy, and their argument against it always harks back to the uniqueness of the individual Thus C G Jung declares that

> "from matters of individual psychology science ought, in fact, to withdraw For, to speak of a science of individual psychology is already a contradiction in terms It is only the collective element in the psychology of an individual that constitutes an object for science, for the individual is by definition a unique reality that cannot be compared with anything else"

This is an obscurantist argument Because an individual is a unique reality, it by no means follows that he cannot be compared with anything else every individual plant, every individual animal is a unique reality but not therefore exempt from comparison and collective study The argument is a reversion to the claim, so often voiced during the controversies about Evolution, that man is, by his nature, fundamentally distinct from all other creatures and an improper subject for comparative study The opponents of the evolutionary theory refused to consider what human beings have in common with other living creatures the argument put forward by Jung ignores what human beings have in common with each other Psychology has in fact concerned itself with individual differences, and has had notable success It may be that the difficulty is verbal, and that Jung means by the psychology of an individual the study of just that which is the essence of each person's total personality, something that would be shattered by analysis and resolution I doubt, however, if his statement is merely a truism, as this explanation would suppose

The dispute has many facets For some, it can become a theological issue For others, the distinction is between the generalising sciences and the historical sciences Popper, whose analysis has been so searching, put forward the view that whereas the generalising sciences are interested in testing universal hypotheses having the character of natural laws, and in predicting specific events, the historical sciences are concerned in explaining past specific events by means of interpretations and specific hypothetical statements about "causes" This view, which is in keeping with Max Weber's, would put clinical psychiatry in the historical class, in so far as it is directed at understanding morbid behaviour, trying to uncover what Jaspers in his elaborate exploration of the matter called "verstandliche Zusammenhänge" It would be improper to put all psychiatry in this class, and I would not have laboured this issue if it were not again evident at the present time that there is a strong move away from the search for general laws, and towards preoccupation with the individual Thus Manfred Bleuler, one of the most prominent of European psychiatrists, declared recently that the most essential feature in the recent development of psychiatry has been that the diagnosis of disease has given place to absorption in the personal tragedy of individuals "das Hauptaugenmerk richtet sich auf Einzelschicksale" (Bleuler 1957) The effect of this movement will, I submit, be retrograde

* * *

I have dwelt so far on prognosis and treatment There is another extensive but rather neglected territory in which few psychiatrists tread a confident path—the alleviation of chronic disorders, and especially chronic schizophrenia The word "chronic" has got a bad name, and many think they can dodge its terrors by submitting "long-stay" for it But changing names has always proved a futile game in psychiatry, and the chronic patients, whatever the euphemism applied to them, remain a vast reproach The Chairman of the Board of Control lately reminded us that the number of chronic patients in England and Wales has remained fairly constant throughout the years, at about 130,000, 85% of the patients in the mental hospitals have been there for more than a year, and 60,000, (i e, two-fifths of the whole mental hospital population) have been there more than ten years, 50,000 of these patients suffer from schizophrenia (Armer 1957) Considered in relation to the general population, there are for every 100,000 people over 16 in England and Wales, 270 in a mental hospital suffering from schizophrenia, mostly in a chronic form It is painfully clear that chronic schizophrenia is an outstanding medical and social issue

Some therapeutic zealots believe that if appropriate treatment, especially insulin-coma treatment, had been administered early to these patients, many of them would not have become chronically ill For this belief there is no adequate foundation We must, unfortunately, reckon with the continuance, for decades at least, of this vast company of more or less incapacitated schizophrenics

It is, however, necessary to distinguish between being chronically ill with schizophrenia and having therefore to be in a mental hospital The attitudes of doctors and of society at large determine whether a person with a long-continued mental illness lives in a mental hospital or in the community. The practice of some countries has been towards increasing mental-hospital care, and of others towards keeping it at a minimum. Many communities have been readier to build and equip medical institutions—hospitals as we know them—than to provide hospitals in the older sense—asylums for the infirm and the indigent—and homes in which the patients could find friendly shelter, as at Gheel.

We are now entering a phase in which we shall be directing our efforts towards keeping patients in the community as long as possible, and if they have to come into hospital, towards returning them to the community quickly. The reasons for this are mixed—awareness of the deleterious effects a mental-hospital environment can have however well ordered it may be and aptly designed for the patients' benefit, regard for favourable social influences which independent life in the community affords, even to the mental cripple, economic advantages for the patient, the taxpayer, and the nation, shortage of nurses, and perhaps some changes in the social ethos. The recent Royal Commission expressed this trend of opinion, in its broadest form, in their recommendation—"there should be a general re-orientation away from institutional care in its present form and towards community care."

This is a hopeful change from that overcautious policy which regarded the mentally ill, especially the chronic schizophrenic, as debarred from society so long as delusions, hallucinations, or peculiarities of conduct were discoverable. But the new policy—I call it new but it was advocated as long ago as 1905—could go to extremes and do much harm. It could also lose its impetus and purpose. Reforms that rest on humanitarian impulse have been most powerful for good, especially in psychiatry, but their momentum has often been lost or their drawbacks been perpetuated when the generation of reformers passed away. The chief safeguard against this recurrent backsliding lies in the accumulation of more precise knowledge, permitting generous aims and lofty principles to be translated into regular procedures that will be applicable even when the reformer's driving force has slackened and gone.

* * *

How much do we know about the issues touching on community care for the chronic schizophrenic? As yet little. Shrewd empiricism and clinical intuition provided, so it was thought, all that we needed for the rehabilitation of the chronic psychotic. There have been preliminary sketches but no finished pictures of the effect of hospital environment upon such patients; few studies of how the patients may be selected, and how prepared, for satisfactory life in the larger community; and only tentative cartoons and inadequate blueprints of the domestic, social, and occupational conditions requisite if they are to keep their heads above water when they have left the mental hospital.

It has long been a commonplace of psychiatric thinking that for many patients there is a critical stage in their mental-hospital stay: if the turning-point is not recognised and the patient then discharged, he will subsequently react to his hospital life and surroundings by becoming worse and the chances of his ever leaving will be very small. What truth there is in this, how the favourable phase is to be recognised, what characteristics of the hospital regime need to be altered to make adverse effects less—regarding these questions there is much guesswork, sometimes ill-assorted with a feeling of certainty "on the strength of my thirty years experience, I am absolutely convinced that . . ." A French psychiatrist, P. C. Racamier, wrote a few months ago that there is no creature in the world more sensitive and vulnerable to his human environment than a schizophrenic, and that a psychiatric ward is a two-edged weapon, potentially therapeutic and potentially "le plus remarquable instrument d'aliénation qu'on puisse imaginer . . . surtout pour ces aliénés achevés que sont les schizophrenes." He states the general proposition that autistic isolation is the only stable relation which a schizophrenic can establish with another person, and declares that it is a "law of sociopathology" that the hospital milieu tends to maintain this morbid stability ("Le milieu hospitalier, l'hôpital tout entier, a tendance a maintenir le status quo stable acquis au prix de la chronicité des malades."). A generalisation such as this, derived from a psychoanalyst's experience as doctor in a mental hospital having no unlocked wards, goes much too far, but it suggests some provocative hypotheses.

To state hypotheses and devise suitable experiments in this field of inquiry is a formidable business, as we and others have found. Social experiments in hospitals will seriously effect the daily care and the disposal of patients, put a strain on the attitudes and sense of security of nurses, and perhaps run counter to cherished clinical beliefs. Only those who would not have to carry out such experiments could be disposed to throw stones at doctors, sociologists, and psychologists for not having accomplished the feat yet.

In the investigations which the Social Psychiatry Research Unit has been carrying out, we have found it necessary at each stage to pass backwards and forwards from laboratory to ward and from ward to laboratory, and to pass from both to the outer world where relatives live and conditions of work and daily life may make or mar the chronic schizophrenic's chance of staying outside hospital for good.

First, there was the inescapable problem of ascertaining the patients to be studied, and then matching one group of them with another. Since there may not be agreement as to which patients are properly diagnosed as schizophrenic, some unambiguous and communicable criteria must be used. Psychologists have applied factorial analysis to rating scales of behaviour, and so worked out diagnostic patterns which can be applied uniformly; the use of these minimised the risk that others who replicate the experiments might obtain discrepant results only because their criteria of paranoid and catatonic schizophrenia differed from ours.

When the patients had been selected—they were men who had been in hospital for years—their mental state and their potentialities for life outside the hospital had to be assessed. Clinical data had to be reinforced by observations on the capacity of the patients to learn and to improve their performance at industrial tasks. The reaction-time of schizophrenics, and the effect of distractions and other extraneous stimuli such as noise had to be determined. Differences were found between paranoid and other schizophrenics which made further laboratory experiments necessary. The effect of incentives had likewise to be investigated under laboratory conditions.

Then there were the chronic patients who had left hospital and managed to stay in the ordinary community. For them methods of investigation and statistical analysis were needed akin to those used for prediction work in criminology. A close study of the family relationships of the schizophrenics and of the community's attitudes to mental illness was called for. Such study is best pursued by the combined work of the anthropologist, the psychiatrist, and the social psychologist

The available techniques and theoretical models are not entirely adequate recent work has shown that the methodological problems are still acute It has been necessary from time to time to leave the more practical problems set by clinical observation and therapeutic intention, and to pursue issues of a more general nature, such as the learning curve of the chronic schizophrenic patients, or the methods of measuring change in mental state over a period of time

The history of these investigations is an object-lesson in reciprocity—reciprocity between fundamental and applied studies, between clinician and social scientist, between laboratory and ward

* * *

I have dwelt perhaps too much on the psychological and social side of the picture Psychiatry is not just applied sociology and applied psychology It has its roots deep in medicine, and most of its surest knowledge derives from the bedside and from physiology, pathology, genetics, and biochemistry It has methods of treatment which are of the same stock as those which have proved themselves in other branches of medicine Its only assured methods of prevention concern mental diseases and defects due to known organic causes It is moreover a practical activity, instinct with humane intention the psychiatrist cannot refuse to act in what he judges to be the most helpful way for his patient, even though the therapeutic procedure is empirical and its benefits still dubious Only a detached spectator, god-like above the battle, could expect the psychiatrist to refrain from giving some form of psychological treatment to patients with distressful anxiety or conspicuous hysteria, though he cannot be certain that it will have effect There are some awful warnings of what a craving for certainty can lead to You may remember the philosopher Cratylus who, as Aristotle tells us, decided never to say anything but what was certainly true, and so he ceased to talk at all and confined himself to wagging his finger

Psychiatry suffers much from hopeful illusions and clichés used as incantations, just as a few decades ago it suffered, even more, from pessimistic and resigned inertia Bleuler's monograph on autistic thinking in medicine is a sustained diatribe against the former of these extremes (Bleuler 1927) Adolf Meyer inveighed against the latter of them Into the stagnant bog of nihilism in treatment we are hardly likely to fall again soon, but we are not out of the other danger

It is easy to lay failings like these at the door of psychiatrists, blaming their lack of scientific training, their loose habits of thought, their incuriosity, their passion for psychoanalysis or for physical methods of treatment, their preoccupation with the fascinating art of
ding other people To think this seems to me
and unjust More important than the deficiencies
the inherent complexity of the problems,
as the outset, the fact that the solution
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become lost in an avalanche of words" The sociological analysis of qualitative data does not reside, as some people assume, in a private world "inhabited by penetrating but unfathomable insights The procedure of even the most perceptive of sociologists must be standardizable and the results of their insights testable by others Science, and this includes sociological science, is public and not private" These words of Robert Merton have a familiar ring The study of human behaviour strongly invites private and discursive interpretations the development of the social sciences, pure and applied, has been a struggle to resist the invitation Psychiatry has made one gigantic effort to escape it, but hardly succeeded psychoanalysis, for all its stimulus and scope, has remained rather private and rather discursive

I have not enlarged on the attainments of psychiatry, its solid groundwork of detailed, minute, and orderly observations, its empirical successes, its accretions through application of the basic medical sciences to clinical problems There are large textbooks and innumerable monographs, compilations, and symposia setting forth this stock of knowledge which stands to the credit of psychiatry It is because of it that the psychiatrist, even the self-critical psychiatrist, feels no need to beat his breast and recite penitential psalms when he meets other doctors There are however occasions, such as this lecture offers, when a review of important areas of ignorance and doubt, and of the reasons for them, seems appropriate

Clearly we are a long way from certainty, and when we meet anyone who is sure that he knows how to tackle the problems of mental disorder and to remedy the failings of psychiatrists and psychologists, we may recall Lord Lansdowne's remark "I wish I could be as sure of anything as Tom Macaulay is of everything" Guessing, too, has its perils and its ardours it takes unkindly to the discipline which is good for it Yet between those who are nearly certain and those who guess much there is the bond which Isaac Newton spoke of "I doubt not we have one common design a sincere endeavour after knowledge, without valuing uncertain speculations for their subtleties, or despising certainties for their plainness"

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ATHEROSCLEROSIS AND ITS CEREBRAL COMPLICATIONS IN THE SOUTH AFRICAN BANTU

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THE high prevalence of coronary-artery disease in more developed communities has focused attention on the causative factors One factor thought to be important is atherosclerosis and hence the interest in the "wide-spread clinical belief that the more severe complications of atherosclerosis such as cerebral and coronary thrombosis are rare among the Bantu" (Higginson and Pepler 1954) This view is supported by Becker (1946), who, in 3000 necropsies on Bantu, held atheroma to have been the direct cause of death in only 0 4%, this is almost the same as Edington's (1954) finding in a survey of necropsies in West African Bantu Again, Humphries (1957) says that in fourteen years' work among natives of South, Central, and West Africa he saw few instances of paralysis due to cerebral hæmorrhage

But Becker (1946) did find atherosclerosis to be common (though not as cause of death) and this seems to have been overlooked For current teaching (e g , *South African Medical Journal* 1957) mentions the "Bantu's relative freedom from atherosclerosis", and Bersohn (1955) is quoted as saying that the aorta of the aged Bantu is comparable with that of a young European Further, according to the Department of Nutrition of South Africa (1956), "heart and arterial disease are very rare among the Bantu" We cannot agree with these views, from our findings in this hospital we consider the true state of affairs in the Bantu to be

(1) Aortic atherosclerosis is common
(2) Cerebral vascular disease is relatively common

Findings

Necropsy Evidence of Atherosclerosis in the Aorta of the Bantu

The serious effects of atherosclerosis are seen in the brain (thrombosis and hæmorrhage) and in the heart (coronary-artery disease)

The findings in table I are drawn from 300 consecutive necropsies in Bantu, over the age of 19, who died in this hospital We have excluded all cases of syphilis or diabetes Necropsies were done (all by one of us) on two-thirds of patients dying in this hospital, which compares well with Higginson and Pepler's (1954) necropsy-rate of 33% Our patients were Bantu from the poorer classes of the midlands of Natal, only 15% came from a city Most live in tribes in rural conditions

Table I shows naked-eye estimates of the degree and extent of atherosclerosis found in the aorta, assessed by a modified form of the grading suggested by Wanscher et al (1951)

Clear = no naked-eye evidence of atheroma
Grade 1 = slight fatty streaking with minimal involvement
Grade 2 = a more obvious atherosclerosis, with plaques tending to be confluent but without obvious ulceration
Grade 3 = severe atherosclerosis including early ulceration
Grade 4 = severe atherosclerosis with ulceration, calcification, and gross scarring

Table I shows that the prevalence of atherosclerosis was significant, even in the younger age-groups, and that its degree and extent increased steadily with increasing age, in the oldest age-groups no-one was found free

TABLE I—PREVALENCE OF AORTIC ATHEROSCLEROSIS IN THE BANTU

Age-group	Sex	Clear (%)	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)	No of patients	Total
20–29	M	26	35	26	4	9	23	41
	F	28	50	22			18	
30–39	M	25	46	8	4	17	24	58
	F	32	32	30		6	34	
40–49	M	19	25	33	17	6	36	56
	F	15	25	30	30		20	
50–59	M	14	41	21	8	16	37	56
	F	5	16	11	52	16	19	
60–69	M		18	27	30	25	40	59
	F		11	21	31	37	19	
70 and over	M			53	29	18	17	30
	F				77	23	13	
No of patients		44	80	73	56	47		300

Cerebral Complications of Atherosclerosis in the Bantu

In 2000 consecutive necropsies in Bantu patients, cerebral hæmorrhage or thrombosis was found in 31, when cases of syphilis and diabetes mellitus were excluded 5 of these 31 necropsies were limited There were 4 men and 13 women with hæmorrhage, and 6 men and 8 women with thrombosis The high proportion of women is noteworthy, since more men than women are admitted to the hospital

Fishberg (1934) points out that cerebral hæmorrhage is by no means rare in patients without hypertension, but there is general agreement that the tendency to cerebral hæmorrhage seems to be greater the higher the blood-pressure Table II shows the number with hypertension in the 31 cases Hypertension was diagnosed when a blood-pressure of over 145/90 mm Hg had been recorded (Wood 1952)

In the 18 hypertensive patients, the pressures were

Diastolic pressure	*Men*	*Women*
90–110 (mild)	1	4
111–130 (moderate)	1	3
131–150 (severe)	2	4
Over 150 (gross)		3
Total	4	14

Table II shows that up to the age of 55 there is no sex difference in the incidence of cerebral catastrophes with or without accompanying hypertension Thereafter, however, the women are more prone to cerebral vascular disease with and without hypertension This sex difference is the reverse of the findings in all more advanced communities (Loder 1953)

Atherosclerosis was present in all but 1 of the 26 patients in whom a full necropsy was done, with the classification of Wanscher et al (1951), 14 had atherosclerosis of grade 3 or 4, 8 had grade 2, and 3 had grade 1 In half the necropsies, atherosclerosis of the cerebral vessels was gross

In 3000 consecutive necropsies in Bantu in South Africa, Becker (1946) found only 1 cerebral catastrophe, whereas in just under 2000 consecutive necropsies we have found 31 such patients—a prevalence almost fifty times greater than that in Becker's series Further, in our series the percentage with cerebral vascular disease found by us in necropsies in Bantu medical patients is as high as that reported at St Bartholomew's Hospital, London—namely, 3 5% (Wilson 1944)

Discussion

Aortic Atherosclerosis

There are few satisfactory records with which to compare our findings

TABLE II—INCIDENCE OF HYPERTENSION IN THE 31 PATIENTS

Age-group	Total	No with hyper-tension	Men	No with hyper-tension	Women	No with hyper-tension
35–44	8	5	3	1	5	4
45–54	6	3	4	2	2	1
55–64	9	5	3	1	6	4
65 and over	8	5			8	5
Totals	31	18	10	4	21	14

The available techniques and theoretical models are not entirely adequate recent work has shown that the methodological problems are still acute It has been necessary from time to time to leave the more practical problems set by clinical observation and therapeutic intention, and to pursue issues of a more general nature, such as the learning curve of the chronic schizophrenic patients, or the methods of measuring change in mental state over a period of time

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It is easy to lay failings like these at the door of psychiatrists, blaming their lack of scientific training, their loose habits of thought, their incuriosity, their passion for psychoanalysis or for physical methods of treatment, their preoccupation with the fascinating art of understanding other people To think this seems to me facile and unjust More important than the deficiencies of doctors are the inherent complexity of the problems, and, as I said at the outset, the fact that the solution of many of the most complex and important depends upon the social sciences, which are still immature Their growth has been rapid, it is true, psychology in particular has moved from strength to strength but they have not crossed some of the awkward hills and ditches that lie in their path and in the psychiatrist's

One of the most distinguished of living sociologists has said that sociology has few formulæ, in the sense of highly abbreviated symbolic expressions of relationships between sociological variables Sociological interpretations therefore come to be highly discursive, " the logic of procedure, the key concepts, and the relationship between variables not uncommonly become lost in an avalanche of words " The sociological analysis of qualitative data does not reside, as some people assume, in a private world "inhabited by penetrating but unfathomable insights The procedure of even the most perceptive of sociologists must be standardizable and the results of their insights testable by others Science, and this includes sociological science, is public and not private " These words of Robert Merton have a familiar ring The study of human behaviour strongly invites private and discursive interpretations the development of the social sciences, pure and applied, has been a struggle to resist the invitation Psychiatry has made one gigantic effort to escape it, but hardly succeeded psychoanalysis, for all its stimulus and scope, has remained rather private and rather discursive

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The Case

Since in published case-histories the doctor rarely appears at all as a person, I had perforce to choose one of my own cases for this study.

I decided to take the first patient I would meet on a certain pre-selected Sunday morning. (I chose a Sunday because I hoped that I would not have to work under as much pressure as on a weekday.)

Early on that Sunday morning the father of a five-year-old girl telephoned me. He said that his little girl had had severe pains in her abdomen since the day before; she had vomited and seemed feverish. I advised him to apply a hot-water bottle to the child's abdomen, and promised to call.

I did not go immediately, but decided to shave, dress, and breakfast before visiting the girl so that I could combine my visit to her with my other visits, without having to go home again. I saw the patient about an hour later. The parents, especially the mother, were very distressed; they feared that the child had acute appendicitis. After examining the child, I told them that I could make no firm diagnosis, and that we could either send the child to hospital, or ask a pædiatrician for a domiciliary consultation. The mother wanted the child to go to hospital immediately, in case an operation were necessary. The child, however, who had listened to the conversation, and who had been in hospital a few weeks before for tonsillectomy, was very distressed at the thought.

In the end, we all agreed to call in the pædiatrician. He came, examined the child with me, diagnosed pneumonia and pleurisy, and suggested antibiotic treatment at home. I gave the child her first penicillin injection, some nursing instructions to the parents, and that completed the treatment for the day. The child eventually recovered and is now quite well.

There had been previous contacts between patient and doctor. The family had moved into the district about six months previously, and become my patients. Their former doctor had advised tonsillectomy, and the child had been placed on a waiting-list. The mother was worried about the child losing her place on the list because the hospital was too far away for her to be taken there. I agreed, after examination of the child, that tonsillectomy was advisable, and was able to arrange it soon in our local hospital. The mother was very grateful for the speed with which arrangements were made.

In this background certain patterns of behaviour had been experienced by everyone concerned, and all had formed certain mental pictures of each other. The mother had seen the doctor fall in with her wishes for treatment of the child, and that he was an obliging man, susceptible to her manifest gratitude. The father, a weak figure, had seen that the doctor complied with his wife's demands. The child had learned that everybody, including the doctor, did what mother wanted. The doctor was pleased, having given satisfaction all round, and acquired a set of " good " (appreciative) patients.

The Patient-group

Although the sick child was the patient to whom the doctor was called, the parents were also involved. They were affected by distressing emotions and had to be dealt with by the doctor therapeutically. Indeed, our case-report would be incomprehensible if it dealt solely with the relationship between the doctor and the child.

Generally, the " patient " is in fact a group of people who are all, in varying measures, affected by the central illness. The peripheral members of the patient-group show mixed somatic and emotional reactions, commonly anxiety, or guilt, or fear of having a similar disease. These reactions both affect the central patient and indicate the need of the peripheral members for treatment by the doctor. To understand and deal with the varied and sometimes opposing needs of the members of the patient-group demands much flexibility.

A few years before the National Health Service, I was called to a child suffering from simple upper respiratory catarrh. To save the working-class mother a further fee, I said that there was no need for me to call again. Some years later I happened to meet the child's grandmother and, remembering that I had not seen the child or the mother for a long time, I inquired after them. The grandmother told me that they had another doctor now, for the mother had felt that by not offering to call again I had not shown enough concern. The child had completely recovered two days after my visit. Obviously, although my treatment of the child had been successful, my treatment of the mother had been clumsy and unsuccessful.

In our present case, had I sent the child straightway to hospital with a bold diagnosis of " (?) acute appendicitis ", the child would have been very unhappy, though the mother's distress would have been relieved. The father would have remained in his ambivalent discomfort of wanting his little girl at home, yet not wanting to contradict his wife. Had I, on the other hand, merely prescribed some appropriate drug and promised to return later in the day, the child would have improved, yet my action would probably have left the mother in a state of doubt and anxiety.

The Immediate Treatment

Our case began with a telephone call, in response to which the doctor advised the application of a hot-water bottle. This simple prescription constitutes the first therapeutic step, the success or failure of which may leave a lasting impression and affect the later steps. It is important, therefore, to examine this advice in more *detail*.

Looking back on the occasion, I remember that the advice was given almost automatically, as if under the pressure of a feeling that something must be done at once in this case. The manifest purpose of the advice was to relieve the child's pain and to reassure the parents. Whether such immediate action and the advice given were best for the child and the parents is a question which can only be answered by scientific argument, and there are undoubtedly as many reasons against as for it. The first treatment decision did not arise out of conscious logical reasoning: it must have been derived from unconscious sources, determined by the personal experiences and attitudes of the doctor, his personality—exactly those qualities that we set out to study.

The doctor showed the same willingness to oblige in the present situation as in his management of the mother's demand for the child's tonsillectomy. He accepted without argument the necessity of visiting the sick child, sensed that the parents were very anxious, and himself became concerned about the child. To continue to be obliging he ought to have visited the child immediately; but he gave himself some very good reasons why he should not. We can see here two conflicting urges: the wish and the disinclination to go immediately.

We might say that the brief telephone conversation about the sick child aroused three major emotions in the doctor.

There was concern about the child, a feeling that, unless something were done, there might be unpleasant consequences—perhaps the child getting worse, or the doctor losing his reputation or the family as patients—in short, *anxiety*.

There was also a dislike of the visit, a hesitation to go immediately, perhaps a feeling that people ought not to bother him so early—or, in terms of basic affects, *hostility*.

Thirdly, there arose the affect of *guilt*, which made him feel that he ought to make up for his not going immediately. He did so by giving the snap advice.

Objectively, there was little cause for anxiety about the child, or for feeling guilty about not going at once. She had been ill for some sixteen hours, and another hour or two would scarcely

Becker (1946), in 3000 necropsies, recorded a high prevalence of aortic atheroma in the older age-groups—e g , 74% in patients over 60, and 56% in patients over 45 He analysed the severity of the lesions in the over-45 group and our findings are set out for comparison our grades 1 and 2 are equivalent to his mild, our grade 3 to his moderate, and our grade 4 to his severe

Degree of atheroma	*Mild*	*Moderate*	*Severe*
Becker s series	58%	16%	26%
Present series	50%	28%	22%

In Becker's series the youngest patient with ulcerative atherosclerosis of the aorta was aged 30, our youngest patient with this degree of disease was 27 Another of our patients aged 45, had had a leg amputated for gross stenosing atheroma of the mouth of the right common iliac artery

Becker found severe atherosclerosis in 26% of the patients aged over 45, but only in 0 4% of the whole series was atherosclerosis a cause of death Although the figure of 0 4% is drawn from patients over and under 45, there remains a significant discrepancy between his two figures which we cannot explain There was no such discrepancy in our series

It seems that our figures for the prevalence of aortic atherosclerosis agree fairly closely with those of Becker who says that " in Bantu subjects the incidence of atheroma of the aorta in the ascending period of life (up to age 45 years) is not far removed from that in other races, and that the incidence of the senescent type may be only slightly less "

Cerebral Vascular Disease

We have already given details of the prevalence of cerebral vascular lesions at necropsy For comparison of findings in Bantu with findings in South African Europeans, it is essential to consider also those Bantu patients in whom it appeared reasonable to assume a vascular catastrophe but who did not come to necropsy or who did not die In this second group, every effort has been made to exclude other diseases capable of causing hemiplegia, and we have excluded all patients with syphilis or diabetes or with abnormalities of the cerebrospinal fluid (except blood) In addition, in an attempt to exclude rupture of a congenital aneurysm, we have excluded all patients below the age of 50 It is conceivable that our criteria have been made over-severe

Within the above limits we found another 37 patients (in 5700 medical admissions) who almost certainly had cerebral catastrophes from atherosclerosis (table III)

In the 21 hypertensive patients, the pressures were

Diastolic pressure (mm Hg)	*Men*	*Women*
90–110	3	2
111–130	4	7
131–150	1	1
Over 150		3
Total	8	13

The combined figures give a grand total of 68 patients admitted for cerebral vascular catastrophes, when correction is made for the limiting age-groups this figure represents 1 5% of all adult medical admissions at risk This is two-thirds of the prevalence of cerebral vascular lesions found in patients admitted to Pietermaritzburg European Hospital (L Fernley, personal communication) But it is probably much below the true prevalence

South Africa is a country of great distances, and no death certificate is required for Bantu dying of natural causes, the patients with cerebral vascular catastrophes who reach hospital represent only that small proportion who are within easy reach of medical help At present there is no method of assessing the numbers who develop hemiplegia and who are buried without record Patients usually come to hospital by bus, this is harder for the paralysed than for other patients

TABLE III—CEREBRAL CATASTROPHES IN PATIENTS AGED OVER 50 (EXCLUDING 31 NECROPSY PATIENTS)

Age-group	*Total*	No with hyper-tension	*Men*	No with hyper-tension	Women	No with hyper-tension
50–54	8	8	6	6	2	2
55–64	9	4	4		5	4
Over 64	20	9	8	2	12	7
Totals	37	21	18	8	19	13

From our findings and those of Becker (1946), we think there is enough evidence to refute the view that the Bantu enjoy any relative freedom from atherosclerosis or from its cerebral complications One interesting finding which needs consideration is the high prevalence of atherosclerosis and its cerebral complications in Bantu women —contrary to the findings in people of European descent (*British Medical Journal* 1955)

Summary

The prevalence of atherosclerosis of the aorta in necropsy examinations in 300 adult South African Bantu shows that aortic atherosclerosis is relatively common in this race 31 patients were found at necropsy to have cerebral hæmorrhage or thrombosis Out of 5700 medical admissions, there were 37 patients in whom the same diagnosis was made but who did not come to necropsy

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THE DOCTOR'S ATTITUDE TO HIS PATIENT

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Homo sum, humani nil a me alienum puto —*Terence*

As soon as we have left the haven of medical school and textbooks and entered practice, we learn to our bewilderment that there is more in treatment than drugs, diets, and surgery Some patients will not improve with correct treatment, others will get better on the wrong treatment, some come to us with deep gratitude when we know we have done nothing for them, while others are full of resentment though we have spent much effort and sympathy Such imponderables as the patient's expectations and fears, the doctor's approach and attitude, and the manner of examination not only influence but often outweigh the conventional treatments indeed, as Balint (1957) has shown

The doctor's personality (or " bedside manner ") is accepted as playing a part in treatment, but is usually thought to be incidental, outside the scope of scientific inquiry

Yet people choose or reject a doctor less for his erudition (which they can hardly judge) than for his " personality ", for that peculiar set of qualities that apparently make medicine an art Patients and doctors alike, for successful treatment, somehow have to suit each other If the doctor's personality and attitudes play a part in medical treatment, then they must be worthy of investigation and evaluation Here I propose to do this, using an illustrative case of the doctor's attitude to the call. Why was the call resented, and whence was the hostility derived?

In his previous dealing with the family the doctor had not minded obliging the child's mother. This time, however, he hesitated. The parents clearly thought that the child had acute appendicitis, and the doctor, too, had provisionally made that diagnosis. Considering the mother's previous reaction to the child's tonsillar illness, it seemed fair to assume that she would again demand operation. The doctor did not like this at all. He hesitated to send the child to hospital, as he might reasonably have done, and preferred a more tedious procedure. The doctor's dislike was directed against the possibility of an abdominal operation in this case.

We can see here a further outcome of his identification with the sick child. His dislike of falling in with the mother's presumed wishes was due to his own then unremembered childhood fears of death and mutilation which aroused anxiety. The doctor's hostility was, at least partly, a defence against this anxiety. The hostility was deviated into a well-rationalised delay.

Hostility always has a definite direction. The two persons, or rather images, against which the doctor's hostility was directed, were the child and her mother. The doctor resented the implicit demand by the mother for an operation—a demand which became explicit later. The limit of his willingness to oblige had been reached, and he said, "Let the mother remain anxious."

The action of delay showed also a hidden hostility towards the sick child, because in waiting there was a risk that the child might get worse. We know that the image of the sick child in the doctor arose out of his identification of the child with his own infantile self. The punitive action against the sick child was equivalent to the punishment he expected, as a child, during attacks of pain. The aggressive forces that had been directed against himself were now directed against the image of the child.

We see now one part of the doctor's mental structure which wanted him to do his duty (namely to go) battling against another part, which wanted him to delay. The result was a compromise, which worked fairly well: the doctor had time to deal with his anxiety, he found an outlet for his resentment by delaying, he could alleviate his feeling of guilt by his snap advice, and the child's pain was relieved and the parents' anxiety lessened. We flatter ourselves by calling such a fortuitous confluence of circumstances good clinical judgment.

Guilt

The feeling of guilt might seem peculiar to our case, because the doctor happened to have had certain guilt-laden events in his childhood. But the guilt was not derived only from the doctor's childhood memories. Like most psychic events, it had multiple sources. The doctor's initial anxiety mobilised hostility, or resentment, which in turn mobilised guilt. But even had there been no resentment, we should have found in our doctor the urge to do something for the child and the parents, arising out of the feeling of "concern", which contains an element of threat. The concern about the patient implies a feeling that not to attend to the patient's need might endanger the doctor—either in his self-esteem or in his relationship to the patient—and this feeling is guilt.

The mobilisation of guilt in doctors by their patients is a general and essential spring of their professional activities. The super-ego function which we call professional conscience or a sense of professional duty is based on the sense of guilt, as is all social conscience. The safeguard against default is not the threat of punishment by external agencies, but the internal threat to our self-esteem. This threat, the expression of the conflict between what we ought to do and what we want to do, is, affectively, guilt. Without it, no doctor-patient relationship in our sense would be possible. If identification is the basis of the adaptation of the doctor in the doctor-patient relationship, guilt is the affective driving force.

It is important for the doctor to become aware of, and to be able to accept, guilt. Even the particular arousal of guilt (as in our case) which represents special pleading is common enough to cause irrational treatment of the patient and unnecessary suffering to the doctor. Some doctors cannot do enough for their patients (not always to the patients' advantage), and wear themselves out for trifles, others even committed suicide because they thought they had not done an operation skilfully enough, expiating unconscious guilt and paying far too high a price.

Our doctor felt that something ought to be done to keep the parents occupied, so he kept them busy with the hot-water bottle. In terms of affects, he felt that they were not doing enough for the child. In keeping them actively employed, he reassured not only them but also their image in his own mind, and, having identified himself with them, he reassured himself. The doctor felt the urge to make them into "better" parents, and thus, by identification, became "better" himself.

This urge to produce "good" images of our patients, and thus a "good" self by identification, may lead to therapeutic overactivity which may be disastrous. The urge for the doctor to be a "good" doctor may make it hard for him to bear that at times he cannot cure a patient, and the hapless patient who will not or cannot get better may be mercilessly punished with drugs, operations, and specialist consultations, and eventually perhaps abandoned altogether. There is an element of such compulsion towards "goodness" in the spot advice in our case, too.

The Clinical Examination

When I arrived at the house I obtained a brief history, I then examined the child systematically, beginning with the throat and ears, and including the chest, nervous system, and abdomen, and taking her temperature and pulse-rate. On reflection later, however, I realised that I had examined the throat, ears, nervous system, and chest rather perfunctorily, but the abdomen minutely, including rectal examination.

In busy general practice one cannot always make detailed general examinations, but when I do so, I take pleasure and pride, as most doctors do, in the skill with which I can perform the various diagnostic procedures, and I am thrilled when I discover an unusual sign which shows that I still possess the technical skill that medical education and experience have taught me. But now I had certainly not used my skill to its best advantage. I inspected, percussed, and auscultated the child's chest, but did not find the abnormal signs which two hours later—when the pædiatrician had demonstrated them to me—were fairly obvious. It seems that my examination was made as if it was meant merely to confirm the already settled diagnosis of acute appendicitis. I was apparently searching for confirmatory evidence, turning a blind eye on such signs as might have indicated a different diagnosis.

Yet, I could not accept the diagnosis of acute appendicitis, though I could think of no other. No doubt the mutilation anxiety was one factor that held me back from accepting the diagnosis, with its consequence of operation. But had this been the only reason, then careful and observant examination of the child would have given me enough clues to pronounce joyfully a different diagnosis, and I should have probed for signs of pneumonia rather than overlooked them.

The doctor's attitude was ambivalent: he wanted to find the source of the child's illness in her abdomen, as in his infant days the source of his pain had been presumed to be in his abdomen, yet he did not want it to be there, on account of his mutilation anxieties. His affectively determined conviction make much difference One may therefore conclude that the anxiety, hostility, and guilt already existed within the doctor, and were waiting only for a particular confluence of events to stir them up, apparently the father's story had all the elements of such a confluence

When, afterwards, I thought about the powerful urge for immediate action, I remembered that in my childhood I had had attacks of abdominal pain, supposed to be caused by "wind," which were relieved by the application of heat They frightened me very much I feared that I might die in one, and that the pain and threat of death were punishment for my misdeeds (mainly truancy from scripture lessons and forbidden sexual fantasies) The father's story struck a chord within me and, though the memories of my own childhood suffering were not then brought into consciousness, some of the affects bound up with them—namely, anxiety and guilt—were re-experienced They gave the impetus to my urge for immediate action, and were the driving force behind the swift, almost automatic advice

Transfer of Emotions

Is this merely an anecdotal incident in a doctor's life? Or is our particular doctor perhaps always driven by such emotional urges and conflicting wishes? Or are more fundamental principles involved?

These affects (anxiety, hostility, and guilt) are not particular to our case or even to our doctor The patient always becomes dependent on the doctor who stirs up emotions in the patient which show up in the patient's behaviour But emotions are not transferred in one direction only The doctor's emotions, too, are stirred up by the patient, and far from being the unconcerned observer, he is indeed a partner in an emotional play and counterplay The doctor may like or dislike the patient, approve of or be disgusted with his story, feel that he ought to fob him off with a tonic or investigate his case in detail, be interested in or bored with him All this is usually, as we know on reflection, irrational It remains to be seen whether the particular effects that we discovered in our doctor were specific to him only or otherwise It is perhaps easiest to show that all doctors feel anxiety about their patients On the instinctual level the mainspring that causes doctors to treat their patients is concern—be it about the patient or the doctor's self-esteem—and concern is closely linked to (and perhaps identical with) anxiety This normal and basic effect is aroused whenever instinctual tension rises, whenever something has to be done

We know from our case-history that there had been a previous relationship between doctor and patients, with certain transference and counter-transference patterns When the father telephoned, the doctor formed a mental image of the sick child, based on these patterns All the facts that the father gave were that the child had vomited and was feverish and in pain, but the image which the doctor formed was of a child frightened by abdominal pain and urging relief, very much like the image of the sick child he had been himself, and this similarity made the doctor feel anxious, hostile, and guilty

The image did not exactly correspond to the real sick child, the doctor at the time had *only two* facts at his disposal, the feverishness and the pain The child's fright, her demand for relief, the similarity of her emotions with those of the doctor as a child were all assumed by the doctor Such distortions of the image of a person we are in contact with are common We need only think of the image a lover forms of his beloved, which to the outsider is often quite unrealistic and fanciful A highly distorted patient image will not easily lend itself to a diagnostic appreciation which would be usefully applicable to the real patient Projection of our past and present emotions on to the image of the patient will influence treatment decisions, and gross distortions of the patient-image may lead to technical errors

Identification

The formation of the object-image—in our case the creation of the image of the sick child in the doctor's childhood image—was the outcome of the doctor's unconscious effort to understand the patient in terms of the life experiences of both himself and the patient He identified the object-image with his own image There were further interlinked identification processes going on at the same time The doctor had gone through periods of anxiety at the illnesses of his own child and could identify himself with the parents All these identifications were part of the process of "understanding" the patient-group

Understanding of the patient means identification with him, and thus identification forms the basis of the doctor patient relationship It is normal and necessary for the doctor to identify with his patient and to show anxiety or concern There are, however, certain dangers

The distortion of the patient-image depends on the extent of identification the greater the identification, the more distorted the image If the extent of identification is not controlled, the image may bear little relationship to the real patient Over-identification may lead to such dangerous assumptions as that what is right for us must be right for others It is probably one of the least successful approaches for the doctor to say to his patient "I have a pain in my back, too, and I put up with it!" In our particular case, the identification of the doctor with the child, the distortion of the patient-image, led to a first-aid treatment of controversial value and not based *on rational or scientific considerations*

In an applied science such as medicine, emotional bias and snap decisions cannot be avoided It is important, though, to remember the existence of bias, distortion of the *patient-image*, and excess identification, so long as we recognise them and do not become too defensive or feel too guilty, they will remain natural deficiencies in our tools, which should not greatly impair the quality of our work It would *help* our understanding of our patients and our relationship with them if we could bring into awareness and control that part of the *identification process concerned with image-formation* But the formation of a distorted object-image and the concurrent identification with it are part of our mental defences, and their laying open is unpleasant and often impossible

It is, however, possible, by a study of the routine snap decisions one makes in medical practice, to obtain at least a dim awareness of one's identification processes, and to beware of such snap decisions

The Delay

Having given the snap advice, the doctor then delayed his departure for an hour or so The reasons were perfectly valid medical practice has to be organised in a business-like way in the interest of doctor and patient alike, a reasonable economy in time and petrol, compatible with the interests of the patient, has to be exercised, and an hour's delay in a case of acute appendicitis is no longer very serious

Yet the call was urgent and aroused enough anxiety in the doctor to cause him to advise first-aid treatment Furthermore, calls at inconvenient hours are common, and I have often gone without delay to urgent calls The above reasons cannot, therefore, be complete

We have seen that the emotional situation which led to the snap advice was complex The snap advice over the telephone not only relieved the doctor's anxiety, but also served as a psychic defence against guilt and enabled him to eat his breakfast in peace The snap advice and the delay in going represent the ambivalence

UTERINE IRRITABILITY

HE CONCEPT AND ITS CLINICAL APPLICATIONS, XEMPLIFIED BY THE OXYTOCIN-SENSITIVITY TEST*

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THE uterus can be stimulated to contract in many ays

Vaginal palpation, dilatation of the cervical canal, or the ntroduction of foreign bodies into the uterus induce contracions or modify the spontaneous rhythm Electrical stimulation f the myometrium or of the cervix will cause local and someimes general contractions Intrauterine infection is said to nitiate contractions Oxytocin, ergometrine, and other xytocic drugs increase the frequency of contractions, while drenaline, papaverine, ether and chloroform anæsthesia, and mylnitrite reduce it Emotional stimuli—such as showing a ypodermic needle to a patient—may excite a contraction he same stimulus in a patient having regular contractions nay cause a contraction to be missed Stimulation of the upples is also known to produce uterine contractions

The magnitude of the stimuli required to elicit a hange in myometrial activity and the response of the terus to a given stimulus are both very variable quanities

The obstetrician wishes to know the overall state of terine irritability Will his patient abort spontaneously?

ESULTS OF OXYTOCIN-SENSITIVITY TEST FOR INDUCTION OF LABOUR BY LOW RUPTURE OF MEMBRANES (AMNIOTOMY)

Test (unit)	No of cases	Time to labour onset (hrs)				Treatment
		Mean	Min	Max	S D	
Series A						
0·01	8	1 5	0	4	1 3	Amniotomy after test
0·02	14	4 7	0	19	6 1	
0·03	14	11 2	1	23	8 4	
0·04	5	11 0	3	30*		
0·05	3	12 3	1	34*		
0 06	2	96	96	96†		
Series B						
0·01-0 03	38	11	86% in labour in 24 hr, amniotomy before test			
0·04-0·06	16	49	54% in labour in 24 hr			
Series C						
Patients treated by oxytocin intravenous infusion until in labour or sensitive to 0 03 unit or less Initially 0 04 or more						
	11	35				

* 1 had oxytocin also
† 2 had oxytocin for four days

Is labour imminent? Will amniotomy or an oxytocic induce labour? To answer him adequately, the causal factors ought to be assayed separately and their composite effect should then be integrated by some master mind Fortunately, however, the patient is a ready-made laboratory and calculating machine which will do the assay and summation and provide the answer directly Since treatments are aimed at increasing or reducing activity, the responsiveness of the uterus to them can be measured by adding or subtracting a known stimulus of the magnitude required to evoke or suppress activity As uterine irritability may vary spontaneously in a matter of hours, a quick test of irritability is more useful than a lengthy assay

This is not to question the need for further research on the prime causes of myometrial hypoactivity or hyperactivity It is always satisfactory to treat disorders by restoring normal levels of constituents where these can be shown to be in excess or deficient, provided that the abnormal levels found by analysis are prime causes and not compensatory changes But the present inadequacy of this approach is evident from the ineffectiveness of substitution therapy as contrasted with the effectiveness of oxytocic therapy and treatment through correction of mechanical factors

There are many ways in which an overall test of uterine irritability could be performed, and we cannot assume that all would give the same or comparable answers (Stimuli which act on the uterus through the mediation of the nervous system or an intermediate endocrine reaction could hardly be expected to bear a constant relation to those that act directly on the myometrium) Two possible methods are

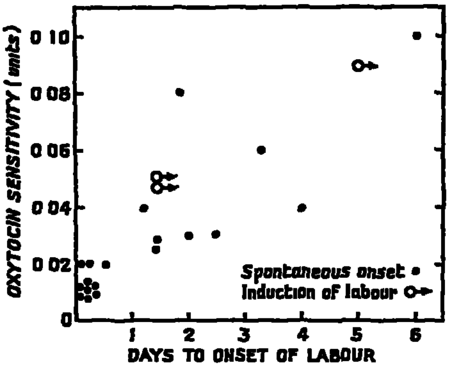

Fig 1—Relation between oxytocin sensitivity and spontaneous onset of labour

Arrowed circles indicate patients in whom the onset of labour was induced artificially This graph, the first evidence of the practical usefulness of the test, was exhibited at the International Congress of Obstetricians and Gynæcologists at Geneva in July, 1954

1 Direct electrical stimulation of the cervix or fundus of the uterus to evoke a local contraction of the myometrium This contraction, however, may not spread to the whole uterus, and is difficult to observe

2 Intravenous administration of minimal doses of oxytocin, 0 01 to 0 1 unit, to cause an increase of uterine activity of observable magnitude In cases of excess activity a reverse measurement can be made by giving minute doses of lævo-adrenaline, which is a potent inhibitor of uterine action

The oxytocin method of assaying irritability is closely enough related to the natural contractile mechanism to be of real value as a clinical sign. Our investigations relating oxytocin sensitivity to the onset of spontaneous contractions, and to the success of methods used to induce labour, support the view that the inert uterus is not myasthenic but merely unable to contract as a whole The reason why it cannot contract as a whole is that the

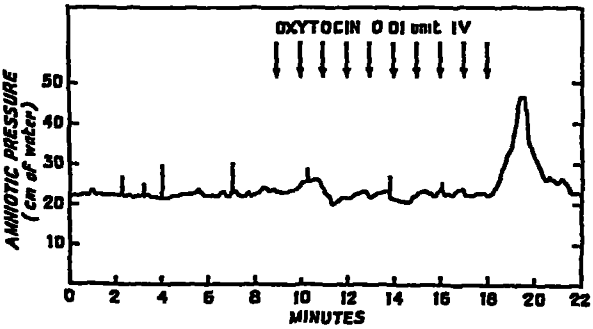

Fig 2—Tocograph recording from patient without spontaneous contractions and with oxytocin sensitivity 0·10 unit.

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* Substance of a lecture and discussion given at Symposion über Wehenphysiologie und Pathologie held by the Mittelrheinische Gesellschaft at Marburg in May, 1957

that the illness was in the abdomen overshadowed his contrary wish, and made him overlook the other diagnostic signs But in spite of this there was doubt, and a desire to achieve a correct diagnosis The signs which he became aware of later, with the pædiatrician, must have been perceived and noted, though unconsciously This was enough in a man with medical training and experience to prevent him from declaring bluntly that this was acute appendicitis The perceptive part of his mental apparatus, his ego, was largely occupied with the building of defences against his anxiety, and only a part of the ego was free to deal objectively with reality

Such a reduction of the ego and narrowing of the sense of reality will happen in the countertransference when unconscious affects are mobilised in the doctor to which he must adapt himself by psychic defences Blind spots will then impair some of his ability to perceive or connect logically A knowledge of one's own sources of anxiety would, of course, help one to recognise the blind spots, or, failing that, a second opinion may help to rectify one's errors It is important to remember that diagnostic and therapeutic errors may arise not only through the limitations of one's knowledge or technique, but also, perhaps largely, through affective impairments of one's perceptive and reasoning ability

Choice of Consultant

My inability to arrive at a firm diagnosis added further to my anxiety Of course, I often have to act therapeutically on an uncertain diagnosis, but in this case it seemed important not to do so I had to be a "good" physician, one who can diagnose and heal

Sometimes we find it easier and sometimes harder to admit medical defeat, or, in terms of the counter-transference, sometimes we can bear to be "bad" and sometimes we cannot I had identified myself with a child who was ill or, in terms of my infantile fantasies, "bad" I had identified myself with the parents too, and the load of guilt in having to be both a "bad" child and a "bad" parental figure would have been too much Previously I transformed the parents into "actively good" parents, for the relief of guilt Similarly, I had to transform myself into an "actively good" doctor

There was only one way of doing so—by calling in a consultant on whose opinion I could rely Psychologically speaking, I was searching for another "good" doctor with whom I could identify myself and thus, by the process of identification, become a "good" doctor myself I put the alternative of hospital or domiciliary consultation before the patient-group but, in fact, the decision had already been taken I knew that the child did not want to go into hospital, and I trusted myself to persuade the mother to my decision

The pædiatrician came I agreed with the consultant on the points he raised, and felt much relieved Anxiety and guilt left me on identification with the consultant It was, after all, not the child's abdomen that was the seat of the trouble, there was no question of operation, and my doubts about the diagnosis had proved that I was a "good" doctor

Why did the doctor call a pædiatrician and not a surgeon into consultation? After all, acute appendicitis was the nearest approach to a diagnosis, and the proper person to consult would have been a surgeon But the doctor tried, even in the selection of his consultant, to fight shy of a diagnosis that might involve operation His infantile mutilation anxieties determined the choice of consultant Again, this affect-determined choice is not restricted to the case under discussion Many patients with hysterical conversions symptoms are sent to cardiologists, neurologists, and surgeons, sometimes with and sometimes without the rationalisation of "to exclude organic disease", but always in the fervent hope that the doctor may be spared the anxiety-arousing, upsetting recognition of emotional tempests in the patient, which in turn, in the counter-transference, stir up the doctor's emotions

The Penicillin Injection

The final step was the injection of penicillin The pædiatrician had advised antibiotics without specifying them It is my habit to use oral antibiotics in children to avoid the hurt of injection ' But now I felt *differently*, I thought of penicillin as a specific for pneumonia, of the saving in the national drug bill, and of the quicker action of parenteral administration, and I felt suddenly very righteous about giving injections

Looking at the case as a whole, the question of operations and maiming has been prominent We remember that the character of my relationship with the patient-group had been determined by my compliance with the mother's wish for tonsillectomy An operation, beneficial as it may be, is mutilating The doctor was used by the mother as an instrument for this symbolically destructive action When he complied, she was very pleased with him and thereby made him feel that he was a "good" doctor The same happened in the case of the appendix The mother hoped, and even pressed, for the relief of her anxiety over the sick child again through attack on the bodily integrity of the child, and again the doctor was to be the instrument Now, however, the doctor could not agree, because this aroused his own mutilation anxieties But he had hostile feelings of his own towards the child, connected with his infantile self-punitive desires

This aggression was successfully repressed until the final act, the injection, when the child could be hurt, yet where the action could be freed from all guilt, as the doctor's rationalisation has shown In fact, the deep justification felt by the doctor for the injection was a form of over-compensation, a way of saying "Not only have I done no wrong, I have done very much right"

The doctor liked his little patient, and wanted to help her and make her well, but through *identification he felt* hostile and unconsciously wanted to hurt her We can often discover aggressive and hostile slants in our treatment activities evil-tasting medicines, reproaches, coldness, excessive brevity, refusals, operations We usually have very good excuses, but the emotional background is one of hostility In our case, the unconscious emotions of liking and wanting to hurt were the expression of two basic drives directed towards the patient—affection and aggression—which had been in conflict Affection had led to identification, willingness to help, concern, anxiety Aggression had led to hostility, delay, guilt Now, they had become fused This fusion was expressed in the helping, yet hurting, act of the penicillin injection

The final act illustrates well the fundamental source of the affects, especially anxiety, which we have studied previously The conflict between libido and aggression, brought about tension, which was felt as anxiety Various other tension-raising and anxiety-producing psychic events in turn happened, as we have seen, and increased the basic anxiety

Summary

In an ordinary illness, a case of pneumonia, the influence of the attitudes of the doctor on diagnosis and treatment have been studied The attitudes are based on the identifications of the doctor with the patient and his family, and the underlying emotional driving forces in the doctor-patient relationship are anxiety, hostility, and guilt They may be used in the service of the patient, or to his detriment, because they may blind the sense of reality in the doctor, unless he is aware of them and their sources

I wish to thank *Mr John O Wisdom*, PH D, and *Dr M Balint* for helpful criticisms of my manuscript

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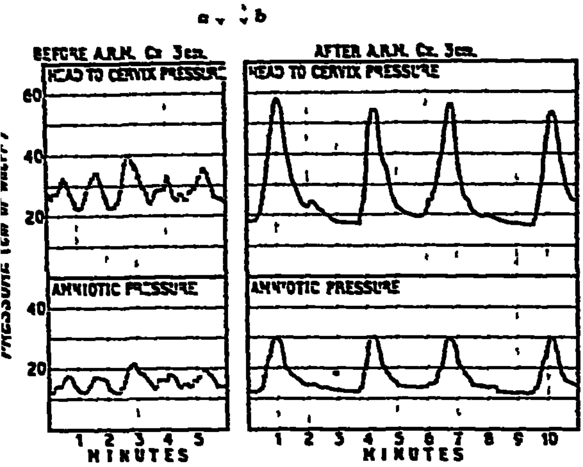

Fig 7—Direct irritating effect of amniotomy resulting from increased pressure on cervix a, before rupture of membranes, b, after rupture of membranes. Cervix 3 cm dilated. There was an interval of only 3 minutes between a and b

est for about an hour The patient is assured that the investigaion is painless and harmless and will aid her treatment

Some form of contraction recorder is placed on the abdomen tocograph) and a recording made for a quarter of an hour or more to note any spontaneous contractions Oxytocin 0 01 unit per ml is prepared in a 10 ml syringe, and the injection is begun at the end of a spontaneous contraction or of any spurious contraction elicited by the exhibition of the syringe. An arm vein is chosen, and care must be exercised to ensure that the patient's clothes do not occlude the venous return The patient is asked to close her hand from time to time during the injections to prevent venous stasis in the arm 0 01 unit is injected at minute intervals until a contraction occurs The total dose given is called the oxytocin sensitivity

The intensity of the contraction elicited can be noted and is often found to be much stronger than the spontaneous contractions which preceded the test. This shows the capabilities of the myometrium and that the spontaneous contractions were not exciting the whole uterus

In some patients with a fast spontaneous contractile rhythm, perhaps one or more weak contractions per minute, a condition called by Alvarez and Caldeyro-Barcia (1954) uterine fibrillation, the test organises this activity into a generalised contraction of normal strength, but in a few patients oxytocin only accentuates the fast rhythm The proper treatment of patients in this latter category has not been determined

The result of the investigations into the value of the test are shown by figs 1–7

Investigations, not reproduced graphically, showed that there was no significant relation between results of the test and the length of labour This was to be expected because the irritability is related to the onset of labour and not to the difficulties to be overcome Further, no significant relation was found between the interval from induction to the onset of labour and the extent to which the cervix is taken up at the time of induction Examination of the cervix did not appear to be a satisfactory alternative to the oxytocin-sensitivity test.

Summary

The biological irritability of the uterus can be assessed by measuring the minimal dose of oxytocin required to produce a perceptible change in myometrial activity The magnitude of dose required is used to specify the irritability

This oxytocin-sensitivity test has useful clinical applications When labour is induced surgically, the results of the test bear a significant relation to the interval between amniotomy and the onset of labour They are also related to the rate of oxytocin infusion required to establish regular labour-like contractions

In normal patients near term, the test indicates how long an interval may be expected before the spontaneous onset of labour If the test shows a constantly low uterine irritability day after day, the infant is likely to be postmature unless labour is induced

Other tests on the same principle are possible but have not been investigated.

The test has applications to the study of uterine action because it provides a method of measuring the change in irritability resulting from administration of drugs or from the application of other stimuli to the myometrium or its nerve-supply

This work was undertaken as part of a programme of obstetric research supported by the Nuffield Foundation and the Rockefeller Fund of University College Hospital Medical School In addition the support and encouragement of Prof W C. W Nixon and the staff of the obstetric unit is gratefully acknowledged.

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BLOOD-GROUPS IN TUMOURS OF SALIVARY TISSUE

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IN view of the increasing evidence of a relationship between ABO blood-groups and certain diseases, I have in the past two years ascertained the blood-groups of patients with tumours of salivary tissue. Of 395 such patients reviewed, the blood-group is now known in 341

The figure shows the general results side by side with those obtained in a control series of 5898 consecutive new registrations of blood-donors at the regional blood-transfusion centre in Glasgow in 1952–55 Statistically the preponderance of group A in the tumour series is highly significant It will be seen that the gain in this group is at the expense of group O

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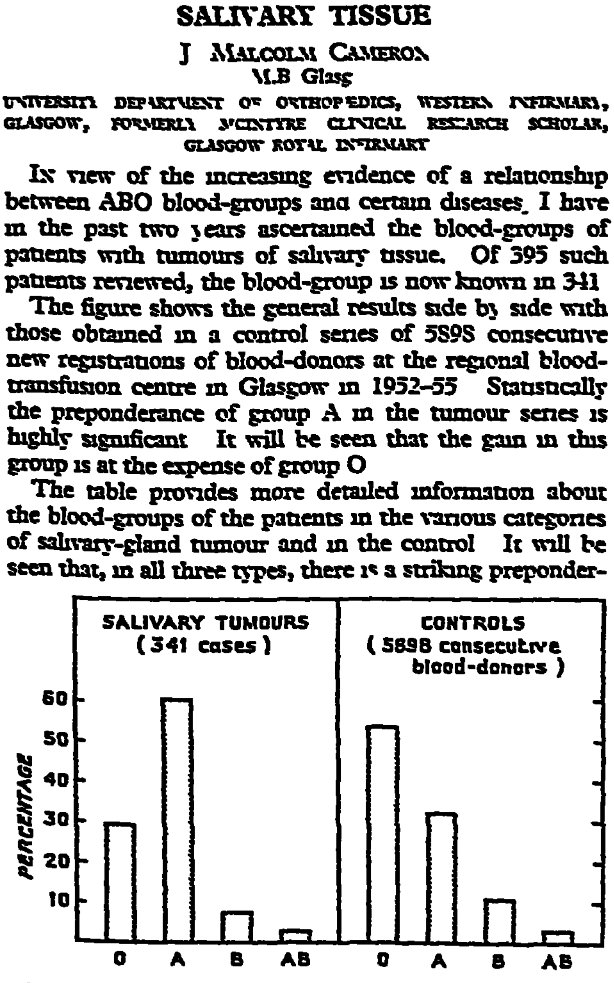

Distribution of blood-groups in 341 patients with tumours of salivary tissue and in 5898 controls

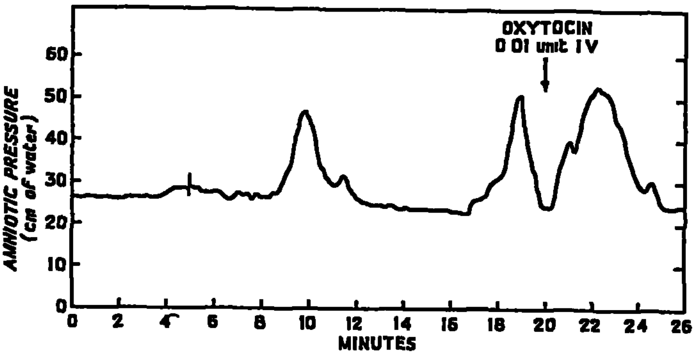

Fig 3—Tocograph recording from patient with spontaneous contraction every 9 minutes and oxytocin sensitivity 0 01 unit

conduction mechanism by which a local contraction spreads to the whole organ is inactive (Csapo 1955, Jung 1956)

Clinical Value of Assessing Irritability

When irritability is considerable, labour is usually imminent, when irritability is less, a longer time will probably elapse before labour begins spontaneously This differentiation enables patients to be kept in hospital or to be sent home When a woman has mild toxæmia or is past term, measurement of uterine irritability helps the clinician to decide whether to induce labour or await its onset When delivery is urgent, labour will be induced in any event, and then the test enables a decision to be made between oxytocin therapy and amniotomy, or possibly a cæsarean section if the uterus is non-irritable and speedy delivery is required Patients with a delayed onset of labour will often be found to maintain the same degree of reduced irritability day after day, as though they had reached the ceiling of their endocrine or other capabilities

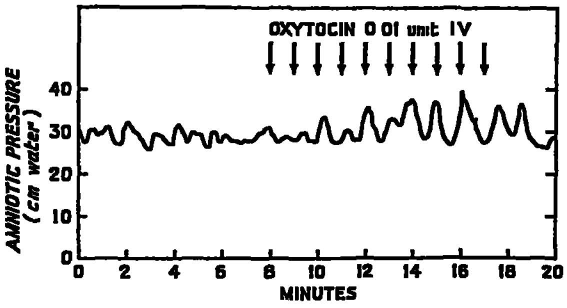

Fig 4—Ineffectiveness of oxytocin in uterine fibrillation.

Methods of inducing labour act because they are biological irritants With the exception of oxytocic drugs, they are weak irritants and therefore ineffective unless the uterus has an irritability approaching that required for spontaneous labour

Amniotomy, which not only acts as an irritant but is also an aid to shorter labour, is undoubtedly the best means of induction, provided the uterus is irritable enough to respond

Rupture of the fore membranes allows the presenting part to descend and, by increasing pressure on the cervix, directly stimulates uterine action (Huber and Beck 1957) Reduction of uterine volume makes the muscle-fibres shorter, and they may thereby become more active physiologically, this effect is principally noticeable in the presence of hydramnios Trauma of the cervix may contribute to irritability chemically or through the nervous organisation Low, opposed to high, rupture of membranes owes its superior effectiveness to the first of these factors

The table and figures show that amniotomy is very successful when the oxytocin test has a numerical value of 0 04 unit or less, and is progressively less successful as the sensitivity approaches 0 08 unit The correlation between the oxytocin sensitivity and the time from amniotomy to th onset of labour is significant at a probability of 200 to

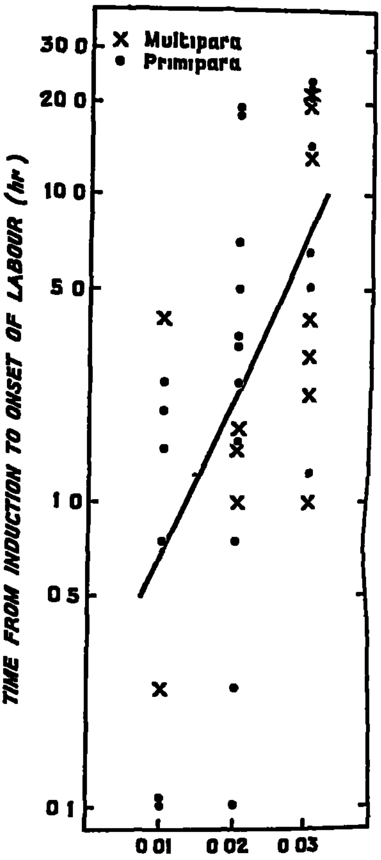

Fig 5—Relation between oxytocin sensitivity and onset of labour after amniotomy of fore membranes in patients more sensitive than 0 04 unit The correlation is significant at 200 1 probability

Oxytocin-sensitivity Test

The patient is in bed and at rest Ambulant patients shoul

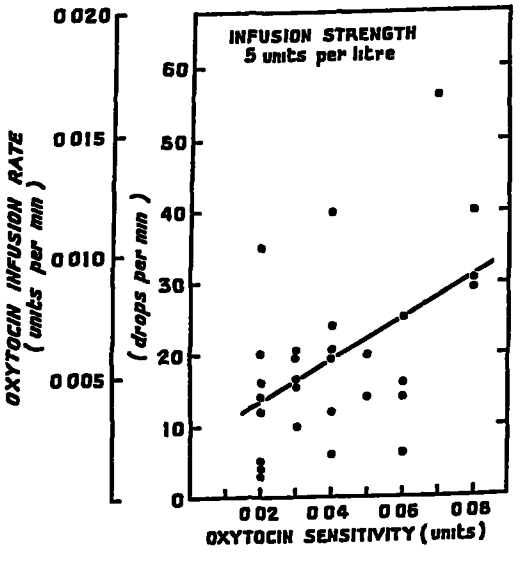

Fig 6—Relation between oxytocin sensitivity and oxytocin infusion rate required for induction The correlation is significant at 50 1 probability

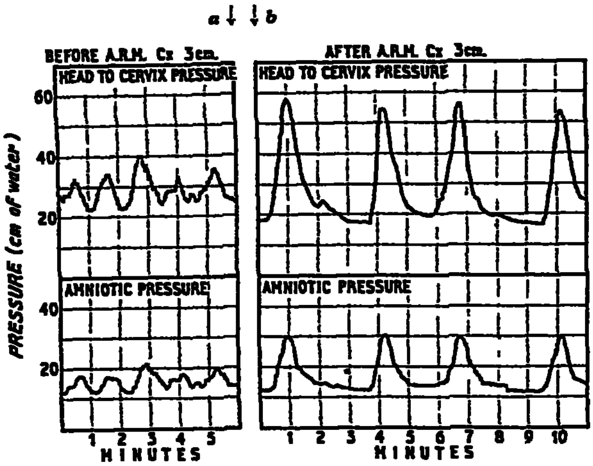

Fig 7—Direct irritating effect of amniotomy resulting from increased pressure on cervix *a*, before rupture of membranes, *b*, after rupture of membranes Cervix 3 cm dilated. There was an interval of only 3 minutes between a and b

rest for about an hour The patient is assured that the investigation is painless and harmless and will aid her treatment

Some form of contraction recorder is placed on the abdomen (tocograph) and a recording made for a quarter of an hour or more to note any spontaneous contractions Oxytocin 0 01 unit per ml is prepared in a 10 ml syringe, and the injection is begun at the end of a spontaneous contraction or of any spurious contraction elicited by the exhibition of the syringe An arm vein is chosen, and care must be exercised to ensure that the patient's clothes do not occlude the venous return The patient is asked to close her hand from time to time during the injections to prevent venous stasis in the arm 0 01 unit is injected at minute intervals until a contraction occurs The total dose given is called the oxytocin sensitivity

The intensity of the contraction elicited can be noted and is often found to be much stronger than the spontaneous contractions which preceded the test This shows the capabilities of the myometrium and that the spontaneous contractions were not exciting the whole uterus

In some patients with a fast spontaneous contractile rhythm, perhaps one or more weak contractions per minute, a condition called by Alvarez and Caldeyro-Barcia (1954) uterine fibrillation, the test organises this activity into a generalised contraction of normal strength, but in a few patients oxytocin only accentuates the fast rhythm The proper treatment of patients in this latter category has not been determined

The result of the investigations into the value of the test are shown by figs 1–7

Investigations, not reproduced graphically, showed that there was no significant relation between results of the test and the length of labour This was to be expected because the irritability is related to the onset of labour and not to the difficulties to be overcome Further, no significant relation was found between the interval from induction to the onset of labour and the extent to which the cervix is taken up at the time of induction Examination of the cervix did not appear to be a satisfactory alternative to the oxytocin-sensitivity test

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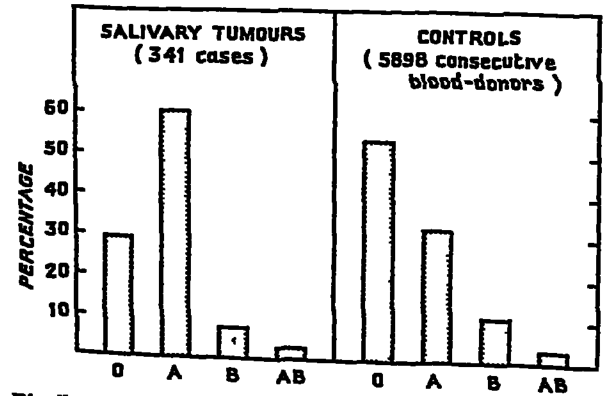

Distribution of blood-groups in 341 patients with tumours of salivary tissue and in 5898 controls.

INCIDENCE OF DIFFERENT TYPES OF TUMOURS OF SALIVARY TISSUE ACCORDING TO BLOOD-GROUPS

Blood-group	Control	Pleomorphic adenoma	Carcinoma	Adeno-lymphoma	Total
A	1906 (*32 3%*)	170 (*57 8%*)	29 (*82 9%*)	7 (*58 3%*)	206 (*60 4%*)
B	637 (*10 8%*)	23 (*7 8%*)	1 (*2 8%*)	1 (*8 3%*)	25 (*7 3%*)
O	3177 (*53 9%*)	92 (*31 3%*)	5 (*14 3%*)	3 (*25 0%*)	100 (*29 3%*)
AB	178 (*3 0%*)	9 (*3 1%*)	—	1 (*8 3%*)	10 (*2 9%*)
Total	5898	294	35	12	341

ance of group A and a corresponding rarity of group O compared with the controls

In analysing the figures, as groups B and AB are relatively constant throughout, group O has been compared with groups A, B, and AB combined together, and the results compared with the control as follows

(1) Pleomorphic adenoma ($\chi^2=57\ 3$) shows a highly significant percentage with group O significantly higher for the controls as against pleomorphic adenoma

(2) Carcinoma ($\chi^2=21\ 9$) again shows a highly significant percentage with group O significantly higher for the controls

(3) Adenolymphoma does not show a significantly lower percentage of group O ($\chi^2=2\ 94$) The indications, however, are that, if the number of patients were increased, significance would be established

(4) All types of salivary tumours were finally considered together and, as would be expected, there was a highly significant ($\chi^2=77\ 9$) percentage, with group O significantly higher for the controls

These findings provide convincing statistical evidence of an unusually high incidence of blood-group A in this series of patients with salivary tumours This is all the more striking because in Scotland group A is found in a smaller proportion of the population than in England

Discussion

From recent investigations into the relationship between disease and ABO blood-groups it appears that these groups are associated with susceptibility to some disorders and relative immunity to others The incidence of group A has been shown to be unduly high in patients with pernicious anæmia (Buchanan and Higley 1921), carcinoma of the stomach (Aird et el 1953), and bronchopneumonia in infancy (Struthers 1951) Group O occurs with excessive frequency in persons with peptic ulceration (Aird et al 1954, Brown et al 1956)

Of these associations the most striking so far published is that between the blood-group and lesions of the stomach and duodenum In the present investigation, however, an even greater excess of group A has been found in patients with tumours of salivary tissue

The selection of a control group presents a well-recognised difficulty (Allan 1954) As a proportion have diseases known to be associated with certain blood-groups, hospital patients are unsuitable I am indebted, therefore, to Dr John Wallace, of the regional blood-transfusion centre in Glasgow, for the data concerning consecutive donor registrations

Summary

The distribution of ABO blood-groups among 341 patients with tumours of salivary tissue was determined The frequency of group A was significantly higher than in 5898 consecutive donors registered at the regional blood-transfusion centre

85 of the patients attended the Western Infirmary and the Southern General Hospital, Glasgow (1950–55), and the others the Glasgow Royal Infirmary (1935–56) I should like to thank the medical superintendents of these three hospitals for access to patients and records, and Mr R A Thomson for considerable help in tracing the Royal Infirmary patients I am indebted to Prof W A Mackey, Prof T Symington, and Dr A Dick for valuable advice and criticism, to Dr I Cook and Dr Robert McAndrew for cross checking most of the blood-groups, to Dr R A Robb, of the department of mathematics in the University of Glasgow, for providing statistical assistance, to Mr P Elliott for the tables, and to all the surgeons and general practitioners who have assisted me throughout the investigations

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DISCREPANCIES IN THE DIAGNOSIS OF GENETIC SEX BY LEUCOCYTE MORPHOLOGY

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The development of cytological methods for the diagnosis of genetic sex has been a great stimulus to the study of human intersexuality Two techniques are available

(1) A high proportion of the intermitotic nuclei of the cells of the skin and many other tissues show, in the female, a characteristic mass of heterochromatin usually lying adjacent to the nuclear membrane Such masses are seen in less than 10% of the nuclei in normal males (Moore and Barr 1954)

(2) Davidson and Smith (1954) described the presence of a nuclear appendage or "drumstick" satellite on the nuclei of polymorphonuclear leucocytes In the normal female more than 6, and in the male less than 6, such bodies were found in a count of 500 mature polymorphs

For the sake of brevity the genetic sex determined by the first method will be described here as the nuclear sex, and by the second as the polymorph sex We record two cases in which a discrepancy was found between the results obtained by the two methods, and we discuss the validity of the leucocyte method

Case-reports

Case 1—A child aged 20 months (described in detail by Ashley and Jones 1958) is considered to be an example of complete sex reversal in that the nuclear sex is male but the phenotype is female and the gonads are histologically indistinguishable from normal infantile ovaries Cells from the skin and buccal mucosa were examined on several occasions, and heterochromatin was always found in less than 6% of the resting nuclei Examination of blood-films, however, showed that "drumsticks" were present in 3% of the polymorphs, a frequency well within the range regarded as female

Case 2—This patient, a case of Turner's syndrome, was seen at the age of 14 months because of poor gain in weight She then weighed 16 lb 5 oz, her birthweight having been 6 lb 14 oz She was undersized, with slight webbing of the neck and marked cubitus valgus Her external genitalia were normal Heterochromatin was found in 4% of the cells of her buccal mucosa, and her genetic sex was diagnosed as *male* Examination of blood-films, however, showed "drumsticks" in 7% of the polymorphs

Fig 1—Neutrophil band cell showing mass of sex chromatin (Feulgen × 1500)

Fig 2—Neutrophil polymorph showing mass of sex chromatin. (Feulgen × 1500)

Fig 3—Neutrophil polymorph showing mass of sex chromatin and satellite drumstick" (Feulgen. × 1500)

Discussion

During the past two years many workers have reported discrepant results in the diagnosis of genetic sex by the two methods

Plunkett and Barr (1956) reported two cases of Klinefelter's syndrome in which the nuclear sex was female but the polymorphs had "drumsticks" in only 6 of 784 cells and 6 of 900 cells This frequency of "drumsticks" is just outside the normal range for females Similar discrepancies were seen by Riis et al (1957) in two cases of Klinefelter's syndrome, by Kosenow (1957) in a case of Turner's syndrome of female nuclear sex, by Wiedemann (1957) in cases of Klinefelter's syndrome, and by Armstrong et al (1957) in a case of true hermaphroditism in which the nuclear sex was female

All these discrepancies were in the same direction—i e, the nuclear sex was female, but the polymorphs showed a smaller percentage of satellites than is normal in the female Our two cases show an incongruity in the opposite sense, the nuclear sex being male but the polymorphs showing satellite frequencies well within the female range Greenblatt et al (1957) have reported the same discrepancy in three cases of Turner's syndrome

Such findings as we have mentioned must raise the question of the validity of each method of genetic sexing vis-à-vis the other

Lennox (1956) has reviewed the subject of nuclear sexing and has discussed the evidence supporting the current view that the "sex chromatin" of the resting nucleus is closely associated, if not identical, with the XX-chromosome complex

Davidson and Smith (1954) were tempted to regard the nuclear satellite as analogous to Barr's sex chromatin, which had become pinched off in drumstick form, and thus analogous to the XX-chromosome complex Davidson (1957), however, has reported discrepant findings in Klinefelter's syndrome and now regards the satellite bodies of the leucocytes as being less closely linked to the XX-chromosome complex than is the nuclear heterochromatin

Briggs and Kupperman (1956) carried out polymorph sexing on twenty abnormal males and forty-one abnormal females and described the results in fifteen cases as "not conforming exactly to the criteria of Davidson and Smith but diagnosable" They emphasised this point and suggested that the incidence of "drumsticks" might have been influenced by the abnormal hormonal environment seen in these cases of aberrant sexual development

Some workers however, still regard the polymorph method of sexing as an accurate indication of the genetic sex Kosenow (1956) recommends that it should be used in preference to skin biopsy or mucosal smear, and cases of aberrant sexual development have been recorded in which the genetic sex has been diagnosed only from blood-films

Carpentier et al (1957) found a sex difference in the leucocytes of the rabbit, a species in which the conventional method of nuclear sexing is inapplicable They claimed to find evidence of the subdivision of the "drumstick" in a manner analogous to the "diplococcus form" of the sex-chromatin body of the nerve-cell described by Crouch and Barr (1954) and they regard the "drumstick" in the rabbit as a cytological expression of the XX complex, as do Sachs and Danon (1956) in man Cytological studies of human blood-cells are scanty Riis (1957) found that sex chromatin could be identified in the lymphocytes of the peripheral blood, and Ashley (1957) reported the occurrence of sex chromatin in the resting nuclei of cells of the blood and bone-marrow in man Sex chromatin was identified in each type of cell of the myeloid series, including polymorphs, which showed also the "drumsticks" of Davidson and Smith (1954) It was identified also in lymphocytes and in early and intermediate normoblasts The nucleus of the late normoblast, which is not in an intermitotic phase, shows no sex chromatin Figs 1–3, taken from a specimen of bone-marrow from a normal fecund female, show masses of heterochromatin beneath the nuclear membrane in mature polymorphs and a band cell, one of the former showing also a "drumstick" satellite

The finding of discrepancies between the nuclear sex and the polymorph sex, together with the cytological demonstration in leucocytes of typical sex-chromatin masses distinct from the nuclear satellite, indicates that leucocyte morphology cannot be accepted as a valid criterion for the diagnosis of genetic sex, and that the satellite body of the polymorph should be regarded as a sex characteristic rather than as the expression of the XX-chromosome complex It is likely, however, that the characteristic leucocyte morphology is genetically controlled This view is supported by the finding of female-type polymorphs in the blood of the male twins in two instances of blood chimerism in man (Booth et al 1957, Nicholas et al 1957) In both these cases it was postulated that female myeloid cells had been implanted in the bone-marrow of the male twins, and that they had retained their ability to produce "drumstick" satellites

In conclusion we suggest that the determination of genetic sex, which has now become an important diagnostic tool, should be carried out by the method, and using the criteria, of Moore and Barr (1954) The buccal mucosa affords the simplest method of obtaining suitable cells, but the skin and many other tissues may be used if available Leucocyte morphology, though clearly deserving much further study, particularly where discrepancies occur, cannot be regarded as a satisfactory routine method

Summary

Two cases are described in which the nuclear sex was male but the polymorph sex female

The validity of the hæmatological diagnosis of genetic sex is discussed, and it is concluded that the "drumsticks" of the polymorphonuclear leucocytes should be regarded as a sex characteristic rather than as the XX-chromosome complex, and that for routine diagnostic purposes the nuclear sexing method is to be preferred

We wish to thank Miss I Forshall, F R C S, and Dr R H White-Jones for allowing us to report case 1, Dr A E McCandless for allowing us to report case 2, and Dr E G Hall for helpful discussion and advice

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CAVERNOUS HÆMANGIOMA OF THE LUNG

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In a review of the literature Stringer et al (1955) collected 140 published cases of cavernous hæmangioma and added 2 of their own In 135 the ages of the patients when first seen had been recorded

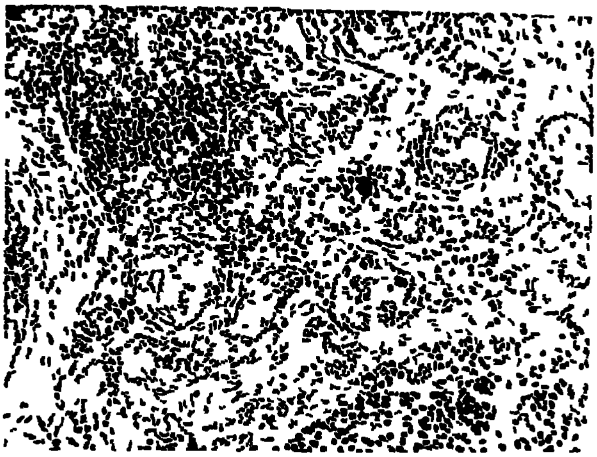
Age	*No of Cases*	*Age*	*No of Cases*
0–7 days	3	31–40 yr	16
7 days–1 yr	3	41–50 yr	19
1–10 yr	11	51–60 yr	15
11–20 yr	23	61–70 yr	4
21–30 yr	40	71–80 yr	1

We report here another case, in a man of 66, which has some unusual features

Case-report

A tall lean shepherd, of 66, complained in 1954 that he had had a cough for many years In 1945 he had coughed up a quantity of blood but had not felt ill and had not sought medical advice In 1949 he had had another hæmoptysis, followed by pyrexia for several days No further attack occurred until 1954, when a bout of hæmoptysis was accompanied by an exacerbation of the cough

No abnormal physical signs were found in the chest The radiologist reported "Hypertensive heart shadow The lung fields show moderate emphysema but no other lesion" It was thought that the hæmoptyses might have been due to epistaxis or to the strain of coughing The patient did not attend at the surgery again, and in 1957 was found dead in bed A coroner's inquiry followed



Cavernous hæmangioma of lung

Necropsy Findings

There were no angiomata on the skin or in the mouth, and there was no clubbing of the fingers Each bronchus contained about 1 oz of liquid blood The one leading to the left lower lobe was a little dilated and its inner surface red and velvety Most of the left lower lobe was red and indurated, and some of the smaller air passages exuded pus On the external surface the affected zone was slightly raised and had a serpiginous margin There was no shrinkage of the lobe as a whole The lung tissue elsewhere showed moderate œdema There was some hypertrophy of the left ventricle (heart 370 g) The coronary arteries were of calcified pipe-stem type, and the descending branch of the left vessel was blocked for about an inch by adherent antemortem thrombus No other significant changes were found

Histology

Bronchus to the left lower lobe—The mucosa was almost fully replaced by a vascular sheet densely infiltrated by plasma cells and lymphocytes, the cells penetrating deeply among the submucosal secretory glands There was no structural arrangement suggesting specific inflammation A smaller air-vessel close by showed the same changes with almost complete blockage

Red zone of the lung—The centre consisted of a cluster of vascular spaces filled with blood and embedded in dense inactive fibrous tissue (see figure) At the periphery relatively normal lung tissue was solidly packed with extravasated blood At the junction of the two zones there was a patchy and fairly dense infiltration by plasma cells There was also a tiny focus of suppuration accompanied by necrosis The lesion was evidently an ancient cavernous angioma, the hæmorrhages from which had led to fibrosis and the migration of chronic inflammatory cells, with a secondary acute infection added

Discussion

Willis (1955) states that hæmangiomata are in practically all cases malformations and not neoplasms They may arise in one particular tissue or as part of a syndrome The tissues which may be affected are the skin, bones, central nervous system, peripheral nerves, and viscera The syndromes are combinations of lesions in the following sites

(1) *Skin and mucosæ*

This hereditary disorder is particularly associated with the name of Osler (1901), who described 3 cases At least four workers had drawn attention to the disease previously *The* essential features are the skin lesions, epistaxis from nasal lesions, and the coincidence in several members of a family Less usually hæmorrhages take place from the trachea, alimentary tract, and urinary tract, and in the brain A detailed survey of 218 families was made by Garland and Anning (1950) and subsequently of a further 20 families

(2) The skin and various viscera
(3) The skin and central nervous system
(4) The retina, central nervous system, and viscera

In the present case there were no angiomatous lesions other than in the lung Until quite recently the solitary hæmangioma of the lung was considered to be very rare

Whitaker (1947) could find only 5 reports and added a further 2 cases Cleland (1948) cited Whittaker's findings and described 1 further case Stringer et al (1955) collected 140 cases and added 2 of their own The first published description is that of Churton (1897), who demonstrated the lungs of a boy, aged 12 years, affected by "multiple aneurysms of the pulmonary artery" The first clinical diagnosis was made by Smith and Horton (1939) and the first successful surgical removal by Hepburn and Dauphinee (1942)

Stringer et al (1955) and other workers call the condition pulmonary arteriovenous fistula The essential disturbance of normal physiology is that the angioma is fed by the pulmonary artery and drained by the pulmonary vein, a shunt being provided for venous blood, which, if large enough, will lead to dyspnœa, cyanosis, finger clubbing, and polycythæmia The last-named may, of course, lead to peripheral thrombosis, cardiac hypertrophy, headache, and so on Hæmoptysis develops in a minority of cases and leads to further difficulty in diagnosis If the lesion is large enough, a loud bruit is discovered over the lesion

In the present case cough and hæmoptysis were the only features The lesion was too small to provide either a serious shunt, an audible bruit, or a lesion visible on radiography The published cases are practically all of grave morbidity in infants in whom the condition was compatible with life for days or weeks, in young persons regarded as the subject of congenital heart-disease, and in adults so incapacitated by defective oxygenation that lobectomy was imperative Whitaker's (1947) case 2, however, a man, aged 33, with lip angiomata, a bruit over the tumour, and worm-like opacities in the lung, was symptom-free when operation was suggested and declined to undergo it

The following details cited from Stringer et al (1955) give some indication of the condition seen in patients aged more than 60

(1) Female, aged 65, disabled by dyspnœa for thirty years, bilateral lesions, no operation

(2) Female, aged 63, with dyspnœa and cyanosis for fifteen years, no operation

(3) Female, aged 66, with pain in the back Discovered at routine radiography, no operation

(4) Female, aged 63, with symptoms since childhood Died at operation

Summary

A man who died of coronary thrombosis, and was known to have had a cough and hæmoptysis without other disturbance, was found to have a small cavernous hæmangioma of the lung

The photograph is by the photographic section of the Royal Society of Medicine

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PHOTOGENIC EPILEPSY INDUCED BY THE PATIENT

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IT has long been known that photic stimulation may precipitate convulsions in persons of epileptic constitution The earliest recorded method was that used by the ancient Greeks when selling slaves in the market (Temkin 1945) The potter's wheel was rotated in front of their eyes In some the intermittent occlusion of the sunlight caused vertigo and occasionally a seizure In recent years this phenomenon has been used as an activator of epileptic discharges in patients undergoing investigation by electroencephalography The source of light is a high-powered stroboscope in which the frequency of the flash can be altered (Walter et al 1946, Gastaut et al 1948, Gastaut and Gastaut 1949) Bickford (1948) studying normal subjects by photic stimulation, noted that in 92% of people the occipital frequencies could be "driven"—that is, the frequencies followed the rate of flashes produced by the stroboscope In many there was an associated subjective sensation of colour which was not unpleasant Abnormal discharges, mainly slow and limited to the occipital region, could be produced in some, and in a few there was evidence of paroxysmal discharge of the whole cortex

It seems remarkable that some epileptics, particularly children, should have discovered these facts by chance, and subsequently should have found themselves compelled to induce epileptic episodes in themselves by producing flickering-light stimulation (Rail and Money 1953, Bickford et al 1953, Robertson 1954) We report two further cases in which epileptic attacks are initiated by self-induced photic stimulation

Clinical Records

Case 1—A girl, aged 7 years, was first referred to one of us (J H H) on June 13, 1956, for an opinion as to the nature and significance of an odd "habit" which her parents had noted with increasing concern This was described as a rapid "flicking" of her left hand, with fingers held wide apart, in front of her eyes She always faced towards the sun to do this and never performed on dull days When she started to "flick", her eyelids blinked synchronously After a few seconds she became motionless and "her eyes go blank as if she was not there" Then she staggered or stumbled On occasions she had fallen down, and once scratched herself severely by falling into a rose-bush The loss of consciousness lasted for only a few seconds, and immediately after the episode "she is back to normal" She induced attacks only with her left hand, though she was naturally right-handed Her parents had never noticed any spontaneous mental lapses The child's "habit" had first been noted about a year previously About that time she had been taken to an ophthalmologist because of a concomitant convergent strabismus For purposes of examination her pupils were dilated with atropine This experience upset her considerably, but unfortunately the parents cannot be sure whether the "habit" started before or after this episode The mother maintained that she could tell if the child had been "flicking" a lot as at these times she was irritable

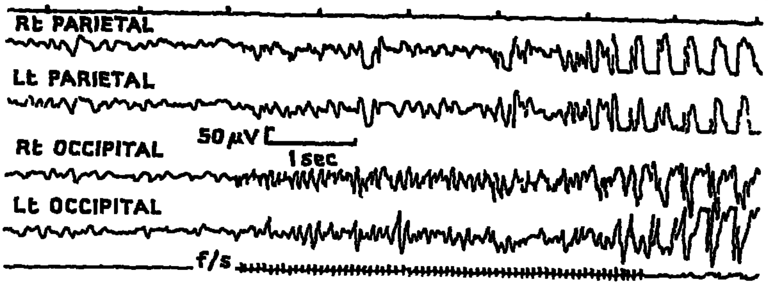

Fig 2—Case 2 Stroboscopic activation at 14–15 flashes a second producing atypical spike and wave which lasted 3–4 seconds

She was an only child Her birth was uncomplicated, and she had had no serious physical illnesses The parents, both very intelligent if fussy people, described her as always having been an excitable and very determined child, who was noisy and overactive and chattered endlessly She ran rather than walked, strove to be the centre of attraction, and had never had any special friends Her only fear was of dogs

There was no family history of epilepsy When the child was 5 months old, her mother had a schizophrenic episode which required 8 months' treatment in a mental hospital, she responded well to insulin therapy and there had been no recurrence From the beginning of this illness a nanny took over the care of the child, continuing until March, 1956—i e , until after the onset of the "hand-waving" The small private school which she attended describes her as impulsive, erratic, and lacking in concentration The staff and her classmates had frequently commented on her "habit" and had made unsuccessful attempts to stop it, as had her parents She once protested to her mother "I just have to do it "

Clinical examination did not reveal any sign of organic disease, she was a big, well-developed girl At the first consultation her general behaviour and demeanour were grossly abnormal She flitted around the consulting-room, apparently ignoring the physician, picked up various objects lying about, and made comments about them without showing any real interest She forced on the onlooker the first impression that here was a spoiled, ill-mannered, and irritating only child

Electroencephalography (E E G) —The resting record was not normal for a girl of her age There was little evidence of a repetitive frequency, but there was a wide range and abnormal bursts of high-voltage spikes, mainly in the occipital region There was no asymmetry (fig 1*a*) Stroboscopic activation at 15–16 flashes a second produced a clear attack of atypical spike and wave lasting for 2–3 seconds (fig 1*b*) Activation at 3 flashes a second had no such effect

Psychological testing showed her to be of superior average intelligence During the test she was tense, distractable, and easily startled by noises On visuomotor tests (Bender-Gestalt) some spatial disturbance was revealed by the transposition of the designs from the horizontal to the vertical Projective tests (thematic apperception and children's apperception tests) showed good general orientation, and no evidence of psychotic trends Her responses gave the impression of a child living in an emotionally cold world The Rorschach test revealed strong compulsive tendencies, and there was a suggestion that her intellectual performance was not up to her capacity Her behaviour in the initial play-interviews was succinctly described by the psychotherapist as identification with the "horror" girls featured in comics, whose adventures she followed avidly and retold with gusto In short, she was boisterous, provoking, and exhibitionistic In these sessions the "flicking" had frequently been observed, and during the first week of October two petit-mal attacks arose spontaneously

Treatment —After the E E G she was given troxidone 150 mg thrice daily from June 25, 1956 Even when the dose was doubled, this drug was without obvious benefit. Early in September, 1956, she was found unconscious in the garden one very bright morning, and she remained in coma for 2 hours A few days later she had a similar but shorter episode It is not known whether these attacks were precipitated by "flicking" On Sept 19 troxidone was stopped and chlorpromazine 25 mg and primidone 125 mg thrice daily were begun Neither these drugs nor the use of rose-tinted spectacles had any appreciable clinical effect Psychotherapy resulted in pronounced improvement in her general behaviour, but it did not reduce the frequency of the "flicking"

Case 2 —A girl, aged 11 years, was admitted to hospital on Aug 21, 1956, because she had been found unconscious in her garden with generalised twitchings of both arms and legs This convulsion lasted about 5 minutes and was followed by a period of unconsciousness which was coming to an end by the time she reached the hospital 6 weeks previously she had fallen down unconscious, she did not twitch in this attack, which lasted only a few minutes

Her parents related that about a year previously, when the family were living in Persia, they had first noticed that the child had developed a peculiar mannerism This was obvious only when there was bright sunshine and when she was out-of-doors She rapidly waved her right hand, the dominant one, to and fro before her eyes, at the same time turning her face up towards the sun She then "appears to go into a trance" On bright days she repeated her habit again and again She first fell down 6 weeks before admission to hospital When her mother reprimanded her, the child said "I can't help doing it" Her mother added "She gets nasty if I try to interfere"

The child's birth had been uncomplicated, and she appeared to develop normally She was pot-trained from the age of 11 days After her 5th birthday she had a series of exanthemata, and also acute nephritis for which she spent 7 months in hospital There, according to her mother,

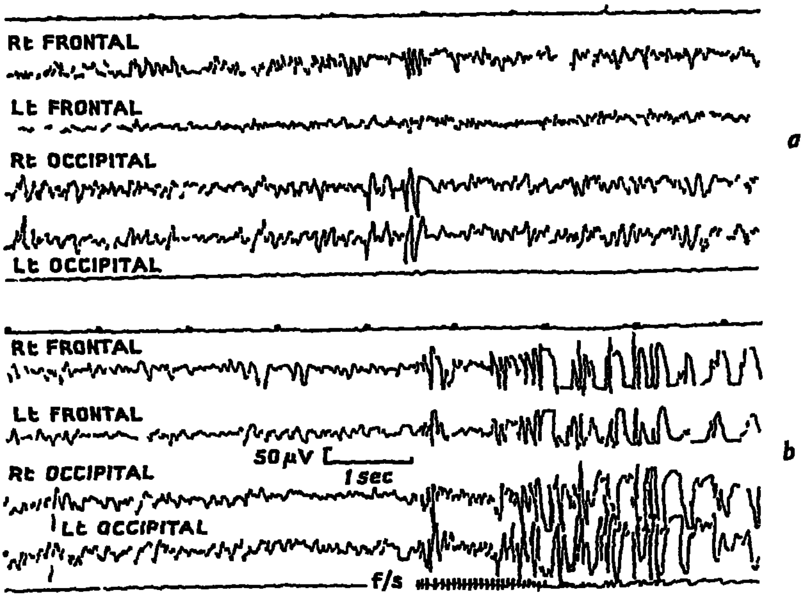

Fig 1—Case 1 (*a*) Resting record showing wide range and abnormal bursts of high-voltage spikes mainly in occipital region (*b*) Stroboscopic activation at 15–16 flashes a second producing atypical spike and wave lasting for 2–3 seconds

she was "spoiled", and subsequently became bad-tempered and selfish at home, though by contrast absurdly generous to strangers Menstruation began in August, 1955, but she had not had a period since May, 1956

There was no family history of epilepsy Her young brother, aged 9 years, was in good health On her own admission the mother was over-protective with both children, and more attached to the boy The schoolteacher described the patient as quite intelligent but very highly strung, she was backward in all subjects, especially arithmetic, and cried easily if reprimanded At home she was often anxious about her schoolwork, and if worried went off her food It was extremely difficult to establish rapport with this mother, who once spontaneously confessed to feeling "cut-off" from people This rather suggests a schizoid personality

Clinical examination revealed no signs of organic disease The patient was a thin, cooperative child who showed apprehension whenever her "habit" was mentioned

Electroencephalography —The resting record was normal with a well-sustained basic alpha rhythm at 10 cycles a second Hyperventilation made little alteration in her record. Stroboscopic activation at 14–15 flashes a second produced an atypical spike-and-wave abnormality, but only when the activation had lasted for 3–4 seconds (fig 2)

Psychological testing was carried out during the child's short stay in hospital She was very tense and showed little perseverance Her intelligence rating was low-average There was no evidence of any visuomotor disturbance In the projective (thematic apperception) test most of the themes which emerged were concerned with failure or the loss of treasured possessions She was a slim, rather angular child with small regular features and fair colouring The movements of her head and limbs tended to be rather jerky A slightly agitated manner revealed her anxiety in the early sessions, but there was, if anything, less shyness than is usual in a girl of this age In fact, this social precocity gave an initial impression of higher intelligence than she possessed In the first psychiatric interview, after recounting something of her life in Persia, she was asked why she was in hospital and explained curtly "I wave my hand" Further questioning elicited the fact that this produced a dreamy feeling, and sometimes fits "I don't like fits, I fall asleep and it takes me an hour to recover" She admitted that she always had dreams during postictal sleep but would not discuss their content. She was emphatic that she never dreamt during ordinary sleep There was no indication that she was upset at returning home from abroad, but a suggestion that she might be worrying about something precipitated a bout of weeping, and with obvious distress the child told in vivid detail how, while she was abroad, one of her favourite horses at riding-school had injured a leg and had to be shot. On her first visit as an outpatient she was again unsure of herself, and her anxiety was revealed in a blinking tic of the right eye and in curious stereotyped movements in which corresponding fingers of her two hands were successively opposed This did not happen subsequently In contrast to the child's customary self-possessed if superficial play and chatter was the gay abandon with which she participated in a game of catch-ball, running and laughing, playfully aggressive and teasing by turn Clearly revealed during these activities was a slight but definite exaggeration of all her movements as if antagonist muscle action was not quite synchronous Even her smile was exaggerated and slow to fade There was no actual motor incoordination She was not observed "flicking" her hand either in hospital or at the clinic A superficial relationship was established easily but did not develop

Treatment —After the E.E.G she was given troxidone 150 mg thrice daily from Aug 20 Neither this drug nor the use of rose-tinted spectacles had any appreciable clinical effect Psychotherapy has proved difficult and, hitherto, somewhat unproductive

Discussion

Both these girls have discovered for themselves the trick of inducing seizures by hand-waving against the sun, and despite criticism continue to do so at fairly short intervals It is interesting to note that an effective rate of stroboscopic activation is around 15 flashes a second, which is a rate that can just be achieved by rapidly waving the five fingers of one hand It is almost certain that, in both cases, seizures arose spontaneously only after being induced Both girls may be considered to have "idiopathic" epilepsy or a striking constitutional tendency to seizures That there is a certain compulsive element in the inducing seems fairly clear from the children's own comments, and in case 1 the child's actual enjoyment is revealed by her remarking during photic stimulation by the stroboscope "that was great", as she squirmed with excitement That this kind of auto-stimulation might be analogous to masturbation had occurred to both sets of parents, but there is no convincing evidence for or against this analogy Again, it is curious that each child invariably "flicked" with the same hand, in one instance the dominant one If this has any significance it may suggest a compulsive ritual, or perhaps a neurophysiological explanation should be sought, in that one half of the visual cortex might be the more sensitive to photic stimulation.

When we come to consider the personalities of the patients the first impression is that, apart from both being reasonably intelligent, they have very little in common—certainly this is true of their manifest behaviour In case 1 the distorted parent-child relationship is of itself sufficient to account for pronounced emotional disorder in the child without invoking "epilepsy" at all, except inasmuch as the child's early behaviour must have modified later parental attitudes In case 2 also, the mother-child relationship is coloured by gross over-protection, and it is not very surprising to observe in the child signs of anxiety and insecurity In both cases, therefore, environmental and constitutional factors almost certainly operate

We have no completely convincing explanation for the time of onset of the "flicking" habit, though it is possible that the impending loss of a nanny in the one case and of a beloved animal in the other may have amounted to situations of emotional stress or conflict

Treatment by drugs, rose-tinted lenses, and psychotherapy has not as yet met with any conspicuous success However, we have not yet exhausted the possibilities of a "trial-and-error" approach, and we intend to follow up carefully the progress of these patients

Summary

The cases of two girls are reported in which epileptic episodes were induced by photic self-stimulation of a compulsive nature

The diagnosis was confirmed by electroencephalography Psychological techniques were used in the assessment of personality

Treatment by physical and psychological methods has proved unrewarding

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Preliminary Communication

A NON-TOXIC COMPLEX FROM PASTEURELLA PESTIS WHICH IMMUNISES BOTH GUINEAPIGS AND MICE

THE following cardinal facts emerge from the extensive literature on immunisation against plague in experimental animals and in man.

1. Mice can be effectively immunised against plague by dead vaccines, but only low-grade immunity is produced in guineapigs by such vaccines.[1]

2. Guineapigs (and mice) are effectively immunised against plague by living attenuated vaccines.[2]

3. The use of living attenuated vaccines in man was prompted by the cogent argument that man should have the benefit of antigens which immunised both mice and guineapigs.[2-4]

4. Mice could be effectively protected by fraction I,[5] the non-toxic envelope substance obtained from saline extracts of acetone-dried *Pasteurella pestis*. This fraction, however, had a much lower protective effect for guineapigs. Some protection in guineapigs was afforded by the so-called "residue antigen" which had a small protective value for mice. The "residue antigen" was that left after extraction of acetone-dried organisms with saline; it appeared to consist of 70–75% of the whole organism.

5. The use of fraction I for immunising man suffers from the possible disadvantage of the low-grade effect observed in guineapigs.

6. Vaccines prepared from whole dead *Past. pestis* are toxic, and this limits the quantity that can be injected.

In view of the efficacy of living vaccines in guineapigs, we examined first the protective activity, in guineapigs and in mice, of fractions obtained from large quantities of *Past. pestis* separated from guineapigs dying of plague. These studies demonstrated the presence in such organisms of a non-toxic complex which immunises both guineapigs and mice. Later a similar complex was obtained from certain cultures in vitro.

OBSERVATIONS

Our method of collecting *Past. pestis* from infected guineapigs has been described elsewhere.[6] An aqueous suspension containing 1 × 10¹⁰ per ml. was treated with ultrasonic waves for one hour at 3°C. The soluble extract, which killed both mice and guineapigs when injected intravenously, constituted about 70% of the whole organism. It would not actively immunise guineapigs in a test similar to that described in the table, and in mice was too toxic for an adequate test to be made.

The residue from ultrasonic treatment was resuspended in water and subjected to ultrasonic waves for an hour at +3°. After removal of the supernatant, which contained very little soluble material, the procedure was repeated. The twice-washed residue contained no intact *Past. pestis* when examined microscopically and in the electron microscope. It constituted about 30% of the whole organism and dissolved almost completely when treated with ultrasonic waves in 0·05*M* $NaHCO_3$ or 0·02M tris(hydroxymethyl)-aminomethane at pH 8·5 or 8·7 respectively. It was examined in toxicity and active-immunity tests with mice and guineapigs at a concentration equivalent to 1 × 10¹⁰ organisms per ml., either as a suspension in saline solution (heated at 60° for an hour) or as a solution in 0·05*M* $NaHCO_3$ buffer at pH 8·5 (filtered through 'Millipore'). Each preparation proved harmless to mice and guineapigs in doses of 0·5 ml. intraperitoneally and 5·0 ml. subcutaneously respectively. The successful results of active-immunity tests in mice and in guineapigs are shown in the upper half of the table.

IMMUNISING ACTIVITY FOR GUINEAPIGS AND MICE OF THE RESIDUE AFTER ULTRASONIC EXTRACTION OF *Past. pestis*

Source and form of the residue[*]	Guineapigs (500 g.)		Mice (20 g.)	
	Quantity[*] injected (ml.)	Survivors/no. injected	Quantity[*] injected (ml.)	Survivors/no. injected
L37 grown in vivo				
(*a*) Solution in 0·05*M* $NaHCO_3$	5·0	5/5	0·1	16/20
	1·0	5/5	0·01	2/20
	0·1	4/5	0·001	1/20
(*b*) Suspension heated at 60°C for 1 hr.	5·0	15/15	0·1	13/20
	1·0	12/15	0·01	8/20
	0·1	4/15	0·001	3/20
L37 grown in vitro† Suspension heated to 60° 1 hr.	5·0	5/5	0·2	8/10
	1·0	5/5	0·1	10/10
	0·1	4/5	0·01	6/10
			0·001	0/10
Tjiwidej, grown in vitro† Suspension heated to 60° for 1 hr.	5·0	5/5	0·2	9/10
	1·0	4/5	0·1	—
	0·1	2/5	0·01	6/10
			0·001	2/10
	Controls	0/20	Controls	0/20

[*] Suspension of *Past. pestis* (1 × 10¹⁰ per ml.) subjected to ultrasonic waves. The washed residue (about 30% of whole organisms) was suspended in saline or dissolved in 0·05*M* $NaHCO_3$ to the original volume.

† Virulent L37 and avirulent Tjiwidej strains grown at 37° in the medium described by Davies[7] and harvested at 20 hr.

Active immunity test—2 subcutaneous injections of protective antigen with a two-week interval—challenge after one week with approximately 100–1000 L.D. of *Past. pestis* (strain L37).

A solution of the well-washed, lipid-containing residue in 0·05*M* $NaHCO_3$ at pH 8·5 showed one precipitation line on Ouchterlony diffusion plates[8] against plague antiserum; this line was common with that produced by the freely soluble fraction I isolated as described by Baker et al.[5] When serum was used, absorbed with an avirulent organism to detect virulence antigens as described by Burrows and Bacon,[9] the solution of the residue also formed a line of precipitation. The relation of these lines to one another and to those virulence antigens previously described[9] is under investigation. In this connection, it is relevant to mention that the solution of the residue in bicarbonate buffer prevented the phagocytosis of *Past. pestis* by guineapig polymorphs; fraction I and the virulence antigens have already been associated with phagocytosis resistance.[9,10]

COMMENT

It appears that the residue from ultrasonic treatment is a complex containing fraction I, a virulence antigen, and at least one other lipid-containing component. We suggest that *Past. pestis* has a cell-wall complex containing lipid, to which fraction I is attached firmly near the cell wall and loosely in the body of the envelope. The same state of affairs probably exists with respect to the virulence antigens. This cell-wall complex with the attached envelope can then be regarded as the best antigenic material for the protection of all species. If it is split by autolysis, acetone drying, and to lesser degree by washing or treatment with ultrasonic waves, then the components lose some of their protective power. This loss may be more apparent in some species than in others, as evidenced by the different protective power of free fraction I for mice and guineapigs.

The protective complex, first recognised in *Past. pestis* grown in vivo, may form the basis of an efficient dead

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vaccine for man Thus it is relatively non-toxic, it has been obtained in a soluble form which can be filtered sterile and freeze-dried, and, unlike previous dead vaccines, it immunises both guineapigs and mice

The practicability of such a vaccine depended on *Past pestis* forming a similar complex under certain conditions in vitro, and recently we have found this to be so Thus, suspensions of similar ultrasonic residues obtained from cultures of the virulent L37 strain and the attenuated immunogenic Tjiwidej strain, were similarly non-toxic and actively immunised guineapigs and mice (see lower half of table†) Such preparations, used alone and with added free fraction I, are being investigated as practical vaccines against plague

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New Inventions

A MACHINE FOR FREEZE-DRYING AND STORING TISSUES UNDER ASEPTIC CONDITIONS

This machine (fig 1) was developed to eliminate the imperfections and to overcome the disadvantages of existing apparatus It was designed especially to avoid the risks of bacterial contamination by carrying out in a single tube with an uninterrupted vacuum the whole process of freeze-drying, desiccation in vacuo over phosphorus pentoxide, storage, and eventual rehydration

Apparatus

The main body of the apparatus consists of a cylindrical manifold with eight ports into which the artery tubes are fitted (fig 2), but it is to the design of the artery tubes that the machine owes most of its originality Fig 3 shows the detail of one of these tubes, the ground-glass joint of cap and tube is in effect a wide-bore tap because, by turning the cap, its port can be made to coincide with the corresponding aperture in the ground-glass surface of the tube

The eight ports for the artery tubes are ground-glass sockets into which fit the side arms on the caps of the artery tubes One end of the manifold leads via a wide-bore tap to a conventional vapour condenser and thence to the pump To avoid dangerous mechanical strains the various articulations are effected by spherical instead of the usual conical ground-glass joints At the other end of the manifold there is an easily removable brass closure which gives access to a boat containing P_2O_5 with a closely fitting ground-glass lid to protect the desiccant from water vapour during the initial stages of freeze-drying This lid can be lifted from the P_2O_5 boat, without disturbing the vacuum, by means of a plunger mounted in a vacuum-sealed shaft on the top of the manifold (fig 2)

Method of Use

Arteries are removed from the donor with full aseptic precautions After being cut into suitable lengths, cleaned, and washed with streptomycin solution to counteract possible coliform contamination during agonal bacteriaemia, they are threaded on plastic formers and placed in the previously sterilised artery tubes One tube serves as a bacteriological control If it is inconvenient to begin lyophilisation immediately, or if only a short time has elapsed between death and the taking of the arteries, and agonal vascular spasm has not yet relented, the tubes are part-filled with sterile saline solution containing streptomycin and are immersed for a few hours in ice and water in the Dewar flask During this stage the contents of each tube are kept sterile by a glass cap that seals the open end of the side channel in the top of the tube (fig 3)

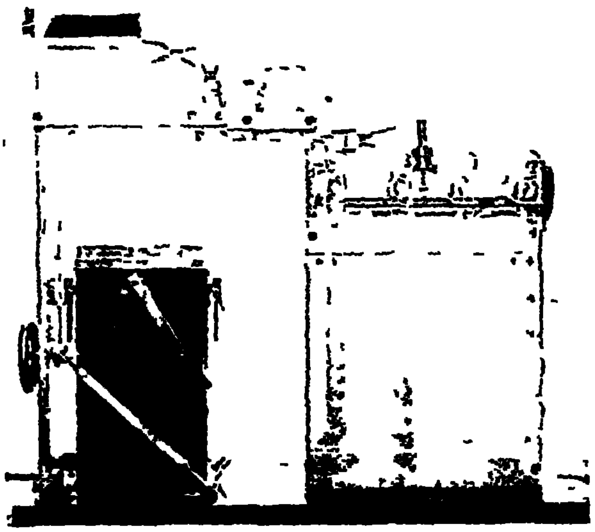

Fig 1—The machine, showing two long and two short artery tubes plugged into the manifold, on top of which is the plunger for lifting the lid of the phosphorus-pentoxide boat Beneath the manifold, hidden from view, is a Pirani gauge On the left the Dewar flask is ready to be raised to cool the condenser

To prepare for the freeze-drying the saline solution is poured out and the tubes are placed in a CO_2-alcohol freezing-mixture in the Dewar flask until the tissues are hard-frozen, the tubes are then transferred to the machine

The freezing-mixture in the Dewar flask is now used to cool the vapour condenser (fig 1), and pumping is begun The latent heat of vaporisation of water from the tissues is sufficient to keep them frozen After 10–12 hours the tap at the end of the manifold is closed, and the lid is then lifted from the P_2O_5 boat

The vacuum is checked from time to time, and, if necessary, pumping is resumed

After four days desiccation is considered to be complete, and the artery tubes are sealed by rotating them inside their caps, to keep the side arms of the caps sterile they are in turn sealed by sterile glass caps fitting over their open ends The tubes containing the dried tissues are stored at room-temperature and have been found to maintain their vacuum

For the freeze-drying of bulky tissues fruit-bottling jars can be used after modification by the addition of ground-glass jointed caps as described above

The body of the machine, when not in use, is kept sterile by formaldehyde tablets placed in glass stoppers plugged into the ports on the manifold

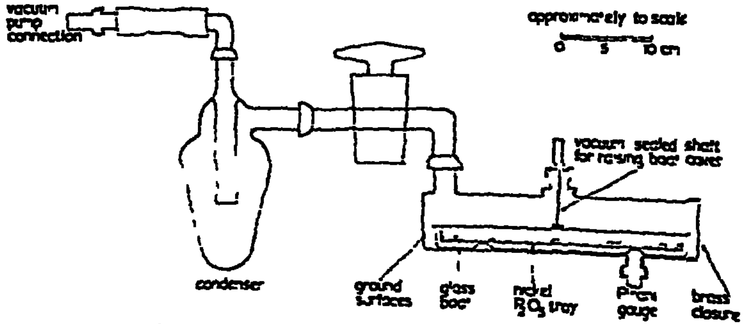

Fig 2—Design of apparatus. Ports for artery tubes are not shown.

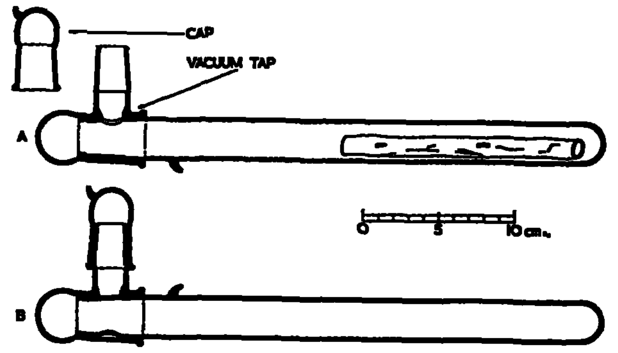

Fig 3—Artery tube Cap and tube form, in effect, a wide-bore tap Rotation of cap to position A opens this "tap" for freeze-drying, and turning to position B seals it for storage The second cap sealing the side arm in B is used to keep this channel sterile

Reconstitution

When the tissues are required for grafting, the cap is removed from the side arm of the tube, and a sterile glass funnel is attached and filled with sterile Ringer's solution (fig 4) The artery tube is slowly rotated inside its cap to allow the Ringer's solution to be sucked in After 20 minutes the artery is removed from the tube, the side branches are tied, and it is ready for grafting

Comment and Results

Bacteriological studies have confirmed that tissues processed in this way remain sterile Macroscopically the arteries after reconstitution are indistinguishable from fresh vessels, and microscopically the only abnormality is pyknosis of the nuclei They have proved satisfactory in use

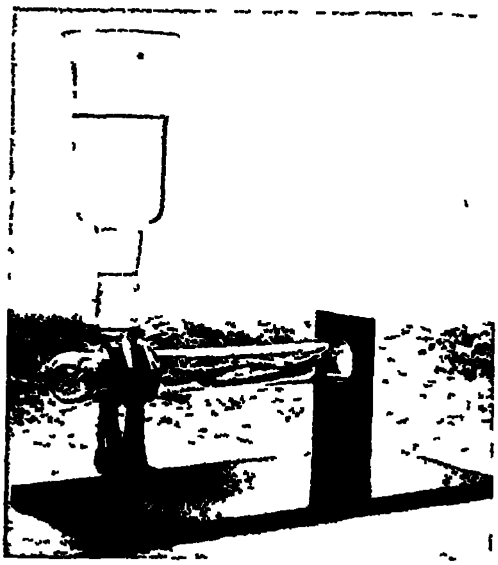

Fig 4—To reconstitute the dried artery, a funnel containing Ringer's solution is attached to the side arm of the artery tube, and the body of the tube is rotated until the hole in the side of the tube and that in the cap begin to coincide, whereupon the fluid runs into the tube and is sucked into the tissue

The apparatus depicted in these photographs was made by one of us (A L) for Prof P Santy at Lyons University We are most grateful both to him and to Prof J H Burn for their encouragement We are indebted to Mr E L Tugwell for the photographs

A M N GARDNER
B M Oxon, F R C S
A LEEMANS

Radcliffe Infirmary, Oxford, and
University Glass Blowing Unit

Reviews of Books

A Short History of Psychotherapy

NIGEL WALKER, PH.D London Routledge & Kegan Paul 1957 Pp 184 25s

CHAIRMAN of the Davidson Clinic in Edinburgh, Dr Walker has written a workmanlike and readable summary of the development in theory and practice of modern psychotherapy He reminds us in his introduction that this, like psychiatry, itself, is not a science but a technique, and the importance of theory to those using a technique is that it should provide suitable explanatory models

The modern semantic treatment of psychological illness is traced from Freud's earliest work on hypnosis, with a brief backward glance at Mesmer, through the period of "primitive psychoanalysis," when Freud was making his discoveries of the Unconscious and of techniques for exploring it The work of Adler, of his modern successor, Carl Rogers, and of Jung is also outlined and the main points of theory and technique are described Suggestion and conditioning, the only trends not derived from Freud's ideas, are given a chapter, describing the Nancy school and Emile Coue on the one hand, and Pavlov and the reflex school on the other

Dr Walker's account of the various schools is throughout objective and free from obvious bias, and his final summing-up of their relative merits and efficacy, and the type of patient most likely to benefit from each, is the more convincing because he pleads no special case

The Bases of Treatment

NEWTON S STERN, M.D, associate professor of medicine, THOMAS N STERN, M.D, instructor in medicine, University of Tennessee College of Medicine, Memphis, Tennessee Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 176 36s

IN framing effective treatment the doctor must have not only proper understanding of disordered physiology but also an imaginative appreciation of the psychological effects of disease This book attempts to cover these important subjects, and fluid and electrolyte balance, diet, the comfort of the patient, and psychotherapy are among its topics The chapter on drugs is largely confined to a consideration of digitalis and penicillin Powerful new remedies may occasionally do harm, and the importance of iatrogenic disease is rightly discussed

The book is written at an elementary level and is designed as an introductory course in the principles of therapeutics Though the intention is sound, the execution is not always successful The ever-present risk of over-simplification has not always been avoided, and we should have preferred a more critical approach to both the results and the limitations of therapy

Extensile Exposure (2nd ed. *Edinburgh* E & S Livingstone 1957 Pp 320 45s)—That there has been a demand for a second edition of Prof A K Henry's now classic monograph will surprise nobody who has had the pleasure and benefit of reading the original He is one of the happy few who can combine anatomy and surgery with artistry, and his highly individual style is displayed in vivid writing and subtle choice of words Most of the original text has been left unchanged, but he has added a section on access at the second left costal arch, and another on the hypogastric route, so that the new edition is nearly twice as long as the first Both new sections are rich fare, and there is now something for all—except perhaps the ophthalmologist All surgeons should read the book There is no pleasanter way of revising anatomy

Hormones in Blood (Ciba Foundation Colloquia on Endocrinology Vol II London J & A Churchill 1957 Pp 409 56s)—Under the chairmanship of Dr A S Parkes a group of scientists from Europe and the United States met last February to discuss circulating hormones, as opposed to their urinary fractions, analogues, or metabolic products The papers have been edited by Dr G E W Wolstenholme and Miss Elaine C P Millar

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THE LANCET

LONDON 1 FEBRUARY 1958

Estimating Fœtal Maturity

ONE of the most difficult decisions the obstetrician is called on to make concerns the termination of pregnancy on account of severe toxæmia, cardiovascular disease, or other maternal disorders If he interferes too early the fœtus may not be viable, but should he delay too long the mother's health may be endangered and the risk to the baby may also increase When the date of the last menstrual period is uncertain the maturity of the fœtus may be estimated by clinical examination, but such estimates are notoriously inaccurate owing to individual variation in such factors as the level of the umbilicus and the thickness of the abdominal wall An X-ray examination is sometimes requested, in which case the radiologist's opinion is usually based on the time of appearance of fœtal ossific centres or the size of the fœtal head, but no great accuracy has hitherto been claimed for this method For example, ROHAN WILLIAMS[1] states that dates of ossification vary widely, he gives the time of appearance of the centre for the os calcis as between the 21st and 29th weeks, and that for the talus between the 24th and 32nd weeks HODGES[2] devised a method based on the size of the fœtal skull, but the particular diameters required cannot always be measured, and in any case there are large biological variations in the dimensions of the fœtus in the second half of gestation

Since 1949 HARTLEY,[3] in Manchester, has carefully studied thousands of antenatal radiographs, correlating all the known or subsequent information regarding the last menstrual period, date of delivery, appearance of the baby at birth, and, in many cases, postnatal X-ray examination He has shown that the times of appearance of the fœtal epiphyses do not vary as widely as was formerly believed for example, he has found that the centre for the os calcis appears consistently between the 24th and 26th week, while that for the talus appears just as regularly between the 26th and 28th week His investigations have also exposed the fallacy of estimating maturity at a later stage of pregnancy from the appearance of the cuboid He has shown how consistently the epiphysis for the lower end of the femur appears by the 36th week, and that for the upper end of the tibia at 38 weeks Previous workers had based their estimates of fœtal maturity mostly on anatomical investigations which by their very nature could not be followed through to postnatal life and which were few compared with the potential material of a large X-ray department When the X-ray department at St Mary's Hospital Manchester, was opened in 1949, very few patients were referred for radiological estimation of fœtal maturity, yet in 1956 this was the examination requested in 25% of 1000 antenatal cases. This indicates the demand for such information and it is also a testimony to the value of HARTLEY's work From the beginning he required a very high standard of radiographic technique, and this was the foundation of his success, for developing fœtal epiphyses are not easily seen, and they need a radiograph of the highest quality on every occasion As a result of painstaking observations on thousands of patients HARTLEY can now estimate maturity in many cases to within a week, and a recent pilot survey showed that 77% of patients were delivered within 14 days of the estimated date

Only two years ago HARTLEY's report would undoubtedly have inspired a greatly increased demand for X-ray estimations of fœtal maturity, but now the reception of his work may be modified by STEWART's[4] account of a possible association between antenatal X-ray examinations and leukæmia in infancy The impact of her preliminary findings has been considerable in one large city a memorandum, signed by obstetricians and radiologists, was circulated to all consultants and general practitioners recommending, among other restrictions, that "routine" pelvimetry and placentography should be stopped Such examinations should never be regarded as "routine", and the memorandum may be more discouraging than its authors intended As STEWART[5] remarked, "antenatal radiography should continue to be regarded as a valuable and essential means of saving life, always provided that it is restricted to cases in which there is 'a definite clinical reason for referring patients for this examination'" WITTS[6] said ' we must balance the risks of X-ray diagnosis and therapy against their benefits The possible 50 cases of leukæmia a year from X-radiation in utero must be set against 439 deaths of mothers in childbirth, 15,829 stillbirths and 9750 deaths in the first week of life in 1955 Obstetricians and radiologists believe that the mortality of mother and child may be significantly reduced by the appropriate X-ray examinations in pregnancy, and that they can save more lives than are likely to be lost from leukæmia."

Treatment of Breast Cancer

UNCERTAINTY has lately prevailed about the best treatment for breast cancer After years of unquestioning loyalty to radical mastectomy, surgical peace of mind has been disturbed by MCWHIRTER's suggestion[7] that axillary metastases are better treated by irradiation without axillary dissection, and, since logic points to the futility of axillary dissection when no metastases exist there, what purpose can radical mastectomy serve? MCWHIRTER[8] has added to these arguments WANGENSTEEN's observation[9] that in 60% of cases with invaded axillary nodes, either supraclavicular or internal mammary glands were also involved, and neither of these groups falls within the scope of radical mastectomy as commonly practised today Describing their technique for the excision of the internal mammary chain, HANDLEY et al[10] reported invasion of these glands in 40% of their series of 57 cases (in 55 of which the primary lesion was in the inner or central part of the breast) McWHIRTER computes that of 1882 cases seen between 1941 and 1947, for only 36% would radical mastectomy have been effective—for those without axillary-node involvement 22%, and those with axillary-node involvement alone 14% On the other hand, 85% of cases were suitable for simple mastectomy and radiotherapy—namely, all except those with distant metastases (15%)

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[1] Williams, E. R. in Textbook of X-Ray Diagnosis; 3rd ed. edited by S. C. Shanks and P. Kerley, vol. 3, p. 5[illegible] London, 1950–51

[2] Hodges, P. C. Amer. J. Roentgen. 1937, 37, 644

[3] Hartley, J. B. Brit. J. Radiol. 1957, 30, 561

[4] Stewart, A., Webb, J., Giles, D., Hewitt, D. Lancet, 1956, ii, 447

[5] ibid p 1355

[6] Witts, L. J. Brit. med. J. 1957, i, 1197

[7] McWhirter, R. Arch. Surg. 1949, 59, 830

[8] McWhirter, R. Brit. J. Radiol. 1955, 28, 128

[9] Wangensteen, O. H. Proceedings of 2nd International Cancer Conference, 1952, 1, 23[illegible]

A strong challenge now comes from the Mayo Clinic[11] where 9649 patients were seen between 1910 and 1954, 9477 of whom were submitted to radical mastectomy alone, the rest to simple mastectomy For the 1918 cases treated in 1941–47, the five-year survival was 59 3%, as compared with 48 1% in McWHIRTER's group treated in the same period BERKSON et al[11] think it is reasonable to suppose that benefit may accrue from significant reduction by surgery of the cancer mass, they hold that the effects of treatment in this respect do not obey an all-or-none law and that inability to remove every cancer cell, including those which may be lurking in supraclavicular or internal mammary regions, cannot be regarded as therapeutic failure Though they concede that axillary dissection might lead to dissemination, as McWHIRTER suggests, they know of no evidence by which this factor may be assessed They also doubt the significance of the improved results noted by McWHIRTER in the group receiving simple mastectomy with postoperative radiotherapy between 1941 and 1945, as compared with those treated in 1930–1934 by radical mastectomy alone and in 1935–1950 by radical mastectomy and radiotherapy[12] They are not convinced that the improvement was really related to treatment since they noted a persistent improvement in survival with each successive quinquennium in their own group —probably the result of earlier diagnosis and earlier surgery From Birmingham also, where 4757 cases were seen between 1936 and 1949,[13] this same trend of improvement was noted with the progress of time The 39 4% five-year survival-rate for the whole period at Birmingham only serves to emphasise the discrepancies between the various groups, for this includes all cases, even those untreated by surgery or radiotherapy, and is comparable with absolute survival-rates from 11 different centres cited by ROSAHN[14] Comparison between the figures from the Mayo Clinic and those from Edinburgh is difficult since at the Mayo Clinic operative deaths have been excluded (though these were few, being 61 or 0 6%) and cases not operated upon were not recorded, whereas 257 inoperable cases were included in McWHIRTER's results ACKERMAN,[15] who had the opportunity of studying McWHIRTER's 1941–47 cases, points out that in at least 220 ovarian sterilisation by irradiation was also performed in addition to simple mastectomy and local irradiation The Birmingham results have both the advantage and the disadvantage of being more comprehensive, for each therapeutic technique and combination is considered separately in relation to the extent of the growth (by Manchester staging), and recurrences are recorded as well as survival-rates—an advantage since closer comparisons may be made, a disadvantage since the analysis is more complicated From these figures radiotherapy associated with radical mastectomy seems to be more effective than radical mastectomy alone, as judged by five-year survival in stage 1 cases, on the other hand, a higher recurrence-rate followed the combination of deep X rays and surgery when nodes were involved—a peculiar equivocation that is hard to explain, just as it is hard to equate these conclusions with ROSAHN's finding either that five-year survivals are not significantly influenced by different methods of treatment or that various treatments influence survival statistics equally[14 16] There is one humbling fact tucked away in the welter of Birmingham figures—only 4 2% of deaths were due to causes other than breast cancer

Staphylococcal Infection in Infancy

STAPHYLOCOCCAL infection originating in maternity hospitals is such a common cause of death and disease that it would be better if only selected deliveries took place in hospital This is the opinion of RAVENHOLT et al,[17] who investigated infection-rates in mothers and babies from fifteen Seattle hospitals after they had returned home 714 families were studied, and it was found that mastitis developed in 31 mothers (4%), and 125 babies (18%) had skin sepsis 41 children born during the period under investigation died before they were 3 months old, 5 of these were proved to have died of staphylococcal disease How long infection with the staphylococcus has been a problem in maternity hospitals, and how serious this problem is, cannot easily be estimated, because there are several forms of staphylococcal infection In the first place there is the outbreak of sepsis, which follows a typical epidemic pattern and is usually controlled only by drastic measures such as closing the unit or wholesale prophylaxis with antibiotics Secondly, there are the spots and sticky eyes which used to be considered quite normal in the newborn, and which still seem to arise at a fairly constant rate The third type is the symptomless colonisation of infants with staphylococci, this has been shown to happen to nearly every baby by the time it leaves hospital

Outbreaks of pemphigus neonatorum were described by RIGBY[18] in 1835 and by TILBURY FOX[19] in 1864, and both these workers recognised the contagious nature of the disease Its staphylococcal origin did not become clear until the nineteen-twenties, at one time it was thought to be syphilitic, and later was said to be caused by streptococci But it was recognised as a definite clinical entity which occurred in epidemics This comparatively clear-cut picture became confused when we began to find out more about the organism Coagulase-positive staphylococci were isolated not only from the lesions but also from the nostrils of about 45% of healthy adults, 75% of nurses, and practically every baby over 4 days old How could one hope to prevent staphylococcal disease when the organism was so widespread? The introduction of phage-typing has shown that there are some kind of tracks in this staphylococcal wilderness In outbreaks of severe sepsis one particular strain, which may not be the most common one, is usually isolated from the lesions The virulence of a strain cannot be safely assessed from its phage-type, but there has been at least one example of a particular type being associated with a capacity to cause disease This is phage-type 80, which has been the epidemic organism in severe outbreaks in Australia, New Zealand, Canada, the United States, and Britain since 1953 Phage-typing has been used to find and exclude or treat carriers of the epidemic strain This method is often successful, and ROUNTREE et al.[20] in Australia and GILLESPIE and ALDER[21] in this country have shown that some nasal carriers can be cleared of staphylococci with ointments containing antibiotics The epidemic strains are nearly all resistant to the common antibiotics, and the more these are used, the more the resistant strains will be selected The clinical form of the disease seems to have changed since the late war Nowadays, pemphigus is uncommon, the virulent staphylococci seem to act on the deeper tissues, producing abscesses, cellulitis, meningitis, osteomyelitis, and pneumonia Staphylococcal pneumonia of infants is being recognised more often, and its origin in maternity hospitals appreciated This is a particularly deadly disease because diagnosis is difficult and the course rapid HARLEY,[22] in Sydney, found that the average time between the onset of pneumonia and death was five days, of 19 infants with this disease, 7 died He recommends that every case of pneumonia in a baby should be treated as staphylococcal until it is proved to have a different cause

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[10] Handley, R S, Patey, D H Hand, B H *Lancet*, 1956, i 457
[11] Berkson J, Harrington, S W, Clagett O T, Kirklin, J W, Dockerty, M B, McDonald, J R *Proc Mayo Clin* 1957 32, 645
[12] McWhirter, R. *Proc R Soc Med* 1948 41, 122
[13] United Birmingham Hospitals Annual Cancer Report 1957, 3, 1
[14] Rosahn, P D *Ann Surg* 1957, 146 899
[15] Ackerman, L V *Cancer*, 1955, 8, 883
[16] Rosahn P D *Ann Surg* 1957, 146, 912
[17] Ravenholt, R T, Wright, P, Mulhern, M *New Engl J Med* 1957, 257, 789
[18] *Lond med Gaz* 1835, 17, 125
[19] *Brit med J* 1864, i, 467, 495, 607

This then is the basis for the opinion of RAVENHOLT et al They were particularly impressed by the danger of hospital-derived staphylococcal disease because they did not limit their investigation to the hospital nursery They extended their studies by the simple (in America) technique of telephoning the mothers in the second month after delivery A considerable amount of sepsis was found to have occurred after the mother and baby left hospital An outbreak in one hospital nursery was followed by an epidemic of sepsis in the mothers and babies at home, caused by an organism of the same phage-type How long these strains persist in the community is not known, but a finding by ROY et al[23] of Toronto may be relevant Antibiotic-sensitivity tests were carried out on staphylococci isolated from children admitted to a pædiatric unit The incidence of resistant organisms was considerably higher in this group than in adults examined in other investigations This, ROY et al say, might be due to the persistence of organisms acquired in maternity hospitals In this country mothers stay in maternity hospitals longer than the four days described by RAVENHOLT, so that relatively more staphylococcal infection will take place in hospital He gives the median time for the development of sepsis as eight days for infants and fourteen for mothers, so we are less likely to miss the immediate post-delivery infections Once the mother and baby have returned home there is little machinery for connecting any illness they may have with the hospital where the confinement took place Staphylococcal disease is not notifiable, and the only follow-up is the routine post-natal examination of the mother and the visit of the health visitor to the home It would be easy for an outbreak of hospital-derived staphylococcal sepsis to pass unnoticed RAVENHOLT and LA VECK[24] in an earlier investigation wrote to twenty-six hospitals in Seattle-King county asking them about their experience of staphylococcal disease They remark that "staphylococcal disease is a major problem in the better hospitals—the ones that have pathologists and good laboratories and a hospital-infection record-keeping system Administrators of hospitals without such resources usually stated that they had no staphylococcal disease problem" Does this apply also to this country?

Annotations

PROSPECT OF POWER

THE statements issued last week about the British and American work on the control of thermonuclear fusion reactions were wisely cautious They were not, therefore, as exciting as some people had forecast a new and abundant source of cheap power is not just round the corner But there can be no doubt that remarkable progress has been made and difficulties have been surmounted which, a few years ago, seemed a complete bar to the extraction of power from this source

To achieve a net gain in energy from the fusion of heavy-hydrogen nuclei (deuterons) it will be necessary to heat the gas to at least 100 million degrees Centigrade and probably more, and one of the enormous problems is how to control and confine the hot gas so that it does not melt and vaporise the apparatus containing it So successfully has this been tackled that in the zero-energy thermonuclear assembly at Harwell temperatures of up to 5 million degrees have been recorded for as long as a few thousandths of a second The smaller device, Sceptre III, at Aldermaston, has got up to about 4 million degrees In the United States the Columbus apparatus at Los Alamos has produced temperatures estimated at between 3 and 5 million degrees for a few microseconds, and in another American machine, oddly named the Perhapsotron, neutron emission was consistent with a temperature of 6 million degrees during a pulse of 60 microseconds Details of these momentous results are recorded in *Nature* of Jan 25

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[20] Rountree P M Heseltine M, Rheuben, J, Shearman, R. P *Med J Aust* 1956 i 528

[21] Gillespie W A. Alder, V G *Lancet* 1957, i, 632

[22] Harley, J D *Med J Aust* 1957 ii 673

[23] Roy, T E. Collins A M, Craig, G, Duncan I B R. *Canad med Ass J* 1957, 77, 844

[24] Ravenholt, R. T, La Veck, G D *Amer J publ Hlth* 1956, 46, 1287

One guide to the performance of ZETA and the other machines is the number of neutrons emitted while the current is flowing in the discharge tube It has yet to be proved conclusively that the neutrons so far observed are the products of thermonuclear fusion There is no doubt that each neutron is generated by the union of two deuterons to form a helium-3 nucleus plus a neutron, but the deuterons may conceivably have acquired the energy necessary for fusion by processes other than heating (such as acceleration by magnetic fields in the discharge) It should not be long, however, before this point is settled, and in Sir John Cockcroft's view it is 90% certain that ZETA's neutrons are true thermonuclear neutrons—in other words, that a thermonuclear reaction has been controlled and a great scientific milestone passed

USE AND ABUSE OF DRUGS BY ATHLETES

OF drug addiction of any kind by athletes there is no evidence whatever in this country, and very little if any in the rest of the world, said Sir Adolphe Abrahams in opening a discussion, in London on Jan 21, by the Society for the Study of Addiction He was referring to a manifesto by the American Medical Association, at its convention last June, which denounced as shocking and vicious the use by athletes of the powerful drug amphetamine Described as by far the most dangerous drug existing today, it can, said the Association, produce violent, rapacious, and criminal behaviour, by converting the ordinary athlete temporarily into the super-type, "pep-up pills" have accounted for the striking athletic records of recent years Athletes, coaches, trainers, and officials indignantly repudiated this charge as ridiculous and without foundation American drug manufacturers issued a declaration claiming that more than twenty years' clinical experience had demonstrated that amphetamine was one of the safest drugs in medical practice

Amphetamine, although previously in use, came into prominence in the 1939–45 war as "energy tablets" given to the Armed Forces Its recognisable effects were to postpone sleep, and to prolong the will to hang on and continue beyond the point at which fatigue would otherwise be overwhelming It elevates the mood and often permits a disregard of physical danger It creates euphoria—a feeling of exhilaration, an increase of confidence, and, as a result, an increased capacity for work, but, as R A F investigators found, the quality of the work is not enhanced, and is in fact a little impaired In saying that, save in the excitable or exceptionally intolerant, no ill effects have been recorded, Sir Adolphe was presumably speaking of single doses, not of the consequences of addiction

He went on to remark that there will always be an ineradicable belief in the existence or discovery of some substance—food or drug—that has the property of increasing muscular efficiency and preventing or delaying fatigue These potentialities have been accorded on the one hand to the simplest materials to be found on kitchen shelves, and on the other to secret concoctions reminiscent of the black magic of witch doctors That effects can be produced is undeniable That these effects result from any active properties in the material administered is a very different question An athlete on the eve of competition is in a highly suggestible state, prepared to confide his well-being to the hands of anybody in whom he has confidence Anything given with sufficient ceremony may be credited with remarkable capabilities, provided that the administrator has the right personality

The Amateur Athletic Association have issued a rule that "drugs may not be used to produce better athletic performances", but their request to the British Association of Sport and Medicine to make clear what is a drug demonstrates the difficulty of drawing a line where legitimate measures end and reprehensible practices—so-called "doping"—begin No reasonable person would object to tea and coffee, although they contain caffeine Alcohol has medicinal properties, and only convinced abstainers would forbid beer, brandy, and wine, which occasionally are of distinct benefit to athletes Are we, asked Sir Adolphe, to refrain from the use of drugs that sharpen the appetite, improve digestion, and so contribute to physical wellbeing? Or from a simple sedative to ensure a good night's rest to an overanxious youngster on the eve of a contest?

It is a common experience that, in moments of stress or emergency, hidden reserves are called on to produce exceptional physical strength through the removal of inhibitions that Nature imposes as a protective mechanism—an index of the margin with which the human machine works Are there drugs that can act in a similar fashion by diminishing sensitiveness, paralysing the consciousness of fatigue, the inhibitions that preserve us from over-exertion, eliminating the functions of judgment and self-protection, while increasing the physical output? It is, doubtless, such drugs that alarmists have in mind when they condemn "doping"

Finally, said Sir Adolphe, if amphetamine and cortisone can directly release another reserve of energy, are they not to be accepted as contributing to normal physiological wellbeing? No criticism was heard of the use of oxygen in ascending Everest, if it were practicable to construct a tunnel with an oxygen-enriched atmosphere (66%) in which runners competed, record performances would be accomplished If drugs can be isolated with a certain stimulating or inhibitory effect of advantage to athletes, with the guarantee that no immediate or ultimate harm is suffered, and fulfilling the ethical requirement that they be free from secrecy and universally available, what objection would there be to their employment? An uncomfortable feeling that it would be unsporting to employ an advantage that the giants of the past lacked?

SERVO MECHANISMS IN GENERAL ANÆSTHESIA

IN ether anæsthesia the blood-level of ether is constantly related to the electroencephalographic pattern[1] Thus the depth of anæsthesia can be measured, and narcosis maintained by means of a servo device arranged to administer further doses of ether in response to changing cortical activity Similar mechanisms can be used for other inhalational agents, and even for intravenous thiopentone[2] Such machines operate intermittently, responding when the level of anæsthesia lightens sufficiently to trigger the mechanism But Bellville and Attura[3] have now designed a servo system in which the "on-and-off" oscillation is eliminated Their servo provides a continuous action which constantly readjusts itself and therefore maintains the patient as nearly as possible at an unchanging depth of anæsthesia With such an apparatus the level of anæsthesia can be more accurately and more quickly determined than by clinical judgment, and the interval between appraisal and correction can be considerably reduced Bellville and Attura consider that servo mechanisms will be of value to the pharmacologist, enabling him to study drug action at or near equilibrium conditions The anæsthetist, however, is often concerned with the action of several drugs in one patient, and, as a human servo, must correlate many different responses from varying parts of the patient. The popularity of servo mechanisms is unlikely to mature in clinical practice, at least until they are complex enough to respond to several variables besides the electroencephalogram

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[1] Faulconer, A, Jr *Anesthesiology*, 1952, 13, 361
[2] Bickford, R. G *Electro-enceph clin Neurophysiol* 1950, 2, 93
[3] Bellville, J W, Attura, G M *Science*, 1957, 128, 827

WATER

IN Britain the system of water-supply has been built up in fragmentary fashion by local initiative, and there are now in all 1250 water undertakings The Metropolitan Water Board (probably the largest such organisation in the world) and the undertakings of Birmingham, Manchester, and Liverpool supply nearly a quarter of the population of England and Wales, and at the other extreme some very small undertakings supply only a few thousand people Since 1945 Governments have been committed to a policy of re-grouping, but hitherto progress has been slow, since it has depended on voluntary schemes, and undertakings are, perhaps understandably, reluctant to negotiate for their own demise The Water Act of 1945 gives the Minister of Housing and Local Government compulsory powers, but if these were widely applied progress would be even slower, since an order, if opposed, has to go through a special, very long procedure

These facts are discussed in an analysis by P E P,[1] which concludes that there should be comprehensive rationalisation and also greater coordination in all matters concerning water-supply, including pollution, drainage, and fisheries Looking to the future P E.P finds a striking paucity of published information on water resources and likely demands The total rainfall in Britain is, on average, about 130,000 million gallons a day About half of this has to be allowed for evaporation and transpiration, leaving about 65,000 million gallons a day Some of this must be left in rivers to provide a minimum flow, some may not be capable of economic development, and some may be polluted beyond reach of economic treatment. At present the public supply system makes available some 2500 million gallons a day, of which about 1600–1700 million gallons is taken by domestic and commercial users and about 900 million gallons by industry and agriculture In addition industry uses amounts far exceeding those obtained from public supplies, but much of this is not consumed (e g, cooling at electricity generating stations) probably, in all, some 2500–3000 million gallons a day is consumed, and well over 20,000 million gallons a day used

In a forecast based on admittedly incomplete data P.E P estimates that the total of water supplied may be increasing by some 2% a year, without allowing for the increase inevitably resulting from slum clearance The country has water enough "The problem for the water industry is primarily an economic one of the capital costs of carrying water from areas of surplus to those of shortage, and of the costs of treating water which is available but in too polluted a state for normal methods of treatment." The water industry has resp[illegible] increasing gross capital expenditure from an [illegible] £17 million in 1948–49 to an average of £39[illegible] 1955–56, but "If the demand for water [illegible] increase, further investment will be necessary [illegible] in public supplies are to be avoided" Other [illegible] possible In the first place, economy in the [illegible] would help, and industry should not draw [illegible] of pure water for purposes where water of [illegible] will serve Secondly, improved measures [illegible] water are allowing it to be taken nearer the [illegible] rivers, rather than by using impounding res[illegible] unpolluted reaches Thirdly, in some parts [illegible] possible to divert winter excess water into [illegible] ground strata

In this country, P E.P concludes, wate[illegible] likely to suffice for foreseeable demand[illegible] rationalisation and extended capital exp[illegible] needed to make sure that it shall be a[illegible] necessary amount and quality

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[1] Policy for Water Planning Jan 27, 1958 Pp 15 2s 6d

STUDY OF CHILDREN

WERE examples needed, child ps[illegible] illustrate very well the fact that progress in [illegible] and more depends on the collaboration of [illegible] of specialist For its practice the pædia[illegible] psychiatrist may require the help of th[illegible] the educational psychologist, and the soc[illegible] the level of theory, biology and ethology [illegible] contributions to the comprehension of c[illegible]

At the International Congress on [illegible] held in Toronto, it was felt that the need [illegible] devoted to the study of normal and ab[illegible] ment, had become imperative, and after [illegible] tion an Association for Child Psycholog[illegible] was founded at a meeting in London [illegible]

The most striking feature of the new [illegible] interdisciplinary character, and its [illegible] well as its membership, will give equal[illegible] scientific and clinical workers conc[illegible] Membership is open to professionally [illegible] in child guidance and child analysis, [illegible] persons in related activities The [illegible] understand, not only hold meetings b[illegible] journal in which discussion as well [illegible] encouraged

Inquiries should be addressed to the [illegible] Hildebrand, PH.D, 8, Brondesbury [illegible] London, N W 2

A CHAIR OF DERMATO[illegible]

THIS week the University of Durh[illegible] Newcastle upon Tyne Hospital [illegible] combined whole-time appointment [illegible] dermatology and consultant dermato[illegible] is to foster research and clinical d[illegible] matology, and their initiative is most [illegible] there is no chair of dermatology in [illegible] a time when the subject and its [illegible] formed by new discoveries and new [illegible] that at least one of our universiti[illegible] the kind of opportunities that go wi[illegible] Many of the processes of disease [illegible] surface of the body, and while ther[illegible] where are increasingly useful to the [illegible] exceptional chances of making

Public Health

THE PLACE OF THE HOME-HELP SERVICE IN THE CARE OF THE AGED

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MOST old people look after themselves, perhaps with some supervision and interest from relatives and a variable amount of help from voluntary bodies When all else fails, however, the local-authority services must accept responsibility for them, and nowadays the old are making ever-increasing calls on these services The home-help organisation, in particular, has been strained by their demands This scheme was introduced to assist domiciliary maternity cases and cases of emergency sickness in the home, and these two groups of patients must still be helped The service is also used for educating problem-family mothers But over the past few years in Sheffield it has become virtually a monopoly of the aged infirm

Our efforts to help old people to remain in their own homes, or to return there as soon as possible from hospital, have resulted in making them increasingly dependent on the home-help service They become unwilling to relinquish it, with the result that the number of new calls is greater than the number that can be removed from the list and the load continues to grow What began as an emergency and temporary support has become the main prop for the care of the aged In consequence the other functions of the service are being curtailed Between 1952 and 1955 the number of chronic-sick cases more than doubled (rising from 737 to 1861), but the number of acute emergencies helped fell from 292 to 109 and the number of maternity cases from 187 to 132 It was therefore decided to review the organisation of the service, and assess its value to old people

Results of Survey

In September, 1956, health visitors visited all the 732 households in a representative sector of the city, where old people were being assisted by the home helps They inquired into the circumstances, environment, and health of the old people no medical examinations were carried out

Marital Status and Age

There were in the group 174 married couples, 84 widowers, 421 widows, 13 single men, and 40 single women (table I) In households where the husband is ill the wife usually manages to look after the home and her husband until she, too, is overwhelmed, and in these households our findings relate to the wife Almost five times as many old women as old men were living alone—an expected result in view of women's longer expectation of life, old men left living alone are more likely to be admitted to hospitals and homes, or taken to live with relatives Solitary men who wish to retain their freedom no matter what the cost in comfort are often found in common lodging-houses In a recent survey in Sheffield * it was found that 86 of the 309 men living in common lodging-houses were over sixty-five The number of women in common lodging-houses is negligible

TABLE I—MARITAL STATUS AND AGE

Age	Married couples	Widows	Single women	Widowers	Single men
90 years and over	1	6	—	—	—
80 to 89 years	38	136	4	33	1
70 to 79 years	88	221	25	46	3
Under 70 years	47	58	11	5	9
Total	174	421	40	84	13

498 of the old people were living alone and of these 160 were over eighty

Disabilities

All but a handful of those interviewed were seeing their doctor regularly, but only 14% were regularly visited by a home nurse Since, in 1955, 54% of the visits of the home nurses were to patients over sixty-five, it was surprising that more of those using the home-help service did not use the nursing service too

TABLE II

Incapacity	No of cases		% of total 732 cases
Immobility due to			
arthritic conditions and joint involvements	194	255	34 8
blindness	39		
gangrene, varicose, ulcers, phlebitis, amputations, &c	22		
Debility due to			
weakness, breathlessness, &c , related to cardiac disease	127	221	30 2
chest conditions	49		
postoperative—e g , cancer	30		
anæmia	15		
Feebleness, dizziness, tremor, unsteadiness, &c , due to ageing of the cerebral arteries	189	189	25 8
Incapacity due to			
depression, psychoneurosis, epilepsy	4	67	9 2
other diseases	63		

229 old people had poor vision and found reading difficult or impossible Some were registered as blind or partially-sighted 117 were very hard of hearing Deafness is perhaps as distressing an affliction as blindness, but it does not interfere with the ability to do housework Their other main disabilities were a compound of those degenerative changes and diseases which make up the syndrome of ill health so restricting to the activities and mobility of the ageing (table II)

Help from Relatives and Neighbours

Independence presumes ability to perform simple, multifarious, everyday tasks of the home Half the old people did no shopping and two-thirds no laundering Some sent their washing to the laundry, and any deficiency was made up by relatives, neighbours, and domestic helps Duties undertaken by relatives and neighbours included washing and the heavier jobs such as carrying coal, decorating, and spring-cleaning For 79 households cooking was done by relatives and neighbours Only 38 were entirely without relatives, 514 had sons and daughters, but 185 had only brothers, sisters, nieces, or nephews Regular visits and help from relatives were given in about half the cases Neighbours in many cases provide help or lessen the loneliness of these old people almost as much as their relatives There was a residue, however, who for one reason or another had to try to stand by themselves—one in three never saw any relatives, one in four had no help from relatives and neighbours, and one in six had no visits from them (table III)

TABLE III—HELP AVAILABLE FROM RELATIVES AND NEIGHBOURS

—	Help and/or regular visits received from				Cases receiving	
	Relatives		Neighbours			
	Help	Visits	Help	Visits	No help	No visits
Married couples	83	115	51	80	68	36
Widows	219	290	204	257	90	51
Single women	13	18	19	22	12	10
Widowers	45	55	45	45	16	10
Single men	7	8	5	4	3	2
	367 (50%)	486 (66 3%)	324 (44 2%)	408 (55 7%)	*189* (25 5%)	*109* (14 9%)

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*Annual report on the health of Sheffield, 1955

Hygiene

We found 48 old people who were living in dirty houses, 77 who were inadequately fed, and 89 showed marked lack of care Some who had obviously lived on a poor diet for a long time professed to a poor appetite and no interest in food, growing disability, inadequate help, and loneliness had resulted in a general deterioration and loss of standards A few were frail and confused and were in need of supervision and help, but we did not find much evidence of obvious mental deterioration Probably this type of case is generally recognised as needing more regular care than can be given by a home-help or home nurse, and relatives assume responsibility or the patient is admitted to hospital

The health visitors thought that 198 cases needed more help, that for 137 cases shorter and more frequent visits would be more useful, and that for 126 cases an evening visit was desirable

Some Difficulties

Though it may seem at first sight that the old people get little help from those who might be expected to give it, there are many mitigating factors In grouped dwellings neighbours themselves are old and dependent on outside help Sons and daughters do not always live near by and may themselves be getting on in years Daughters and daughters-in-law, who carry most of the burden, sometimes have considerable family responsibilities, may be working or be in poor health Too often their task is a thankless one, for many old people become difficult and ungracious There are thus ample reasons why the local authority is obliged to help

Many difficulties are encountered in providing a domiciliary service Sheffield employs about 300 home helps, full- or part-time, yet we are failing to meet all the needs of old people

It is tempting to suggest setting up a register of people over sixty-five, who would be under regular supervision, so that wherever need existed it could be met Apart from the fact that such a procedure would be resisted by many vigorous old people who are in no way disposed to have intimations of mortality thrust upon them prematurely, the cost of the labour force required would be difficult to justify

Old people can all have medical care as a right, and home nursing at the request of their general practitioner enough domestic help, a more general and nebulous commodity, cannot always be found for them, yet this is the king-pin of the care for the aged

Kind of Help

The help needed by the elderly infirm in their own homes ranges from someone who will regularly spend a few hours doing the type of housework which necessitates kneeling or stretching, to someone who will pay daily visits and run through the gamut of duties such as would be undertaken by a solicitous relative This will include washing, shopping, cooking, help with bodily cleanliness and simple nursing services It may include advice on personal business matters, such as pension arrangement or payment of bills in short, the home-help service must provide a comprehensive type of social service Often the provision of help may be nothing but a form of delaying tactics against the day when an elderly person, who wishes to remain independent as long as possible, is taken to live with a married son or daughter, is obliged to ask for a place in an old persons' home, or when infirmity demands removal to hospital Provided the help given is sufficient, the aim of promoting and prolonging an old person's independence is socially and ethically desirable from every point of view

Recruitment

Home helps are largely drawn from the 12 million women in England and Wales between the ages of twenty-five and sixty-five Many of the women in this pool are fully occupied looking after children and husband Old people's homes, hospitals for the elderly chronic sick, canteens, light industry, and the distributive trades all compete for the type of woman suitable for the home-help service This has been recognised by some authorities, who have given their home helps a status and conditions of service that attract the right type of women to take up the work, to some extent at least, as a vocation. Unless a home-help service sets out to be something more than a service of domestic charring, it will not only fail to meet all the needs of old people but will also be in constant competition with private households and hospitals which employ domestic help A home-help service, if it is to become a real social service, must be able to attract women who are balanced and mature enough to handle the elderly with patience, who have enough intelligence and understanding to relate their behaviour to the process of ageing, and who can provide comfort and security as well as competent help

Cost

According to the report of the National Corporation for the Care of Old People for 1956, to keep an old person at home when it is necessary to provide a home nurse, a full-time home help, and night service, will cost more than a hospital bed Superficially it might seem uneconomic to provide a service for one old person in this way, but there is an analogy between the home help given on this scale for a limited period and the case of the seriously ill person who requires to be " specialled " in hospital To provide a costly service indefinitely for an old person at home is, of course, another matter and would be economically impossible

When comparing the cost of looking after an old person at home with hospital care, the average cost per patient must be used and not the cost for the exceptional case In a sample of 200 of the 732 people in this survey only 18 were found to have home-nursing visits as well as a home help The highest total weekly cost of providing home help and home nurse when both were visiting was £2 14*s* 10*d* —for an old person who had daily general nursing and a home help one full day per week. The lowest figure of 15*s* 6*d* was for a patient who had a weekly injection and the aid of a home help for one half-day per week. In the first example a bedridden person is being kept out of a hospital bed with the help of a home nurse, relatives, or friends, supplemented by a home help, and in the second the small amount of help given to an ambulant patient may well be the alternative to removal to an old persons' home

The difficulty arises where the service is stretched too far in an attempt to cover all who have asked for help It becomes inadequate with the result that the old person who is left without relatives and friends must inevitably be removed to hospital almost as soon as she becomes confined to bed Thus of the 732 people in the survey only 30 were confined to bed or wheelchair, and it is obvious that a further number might have been kept in their own homes if the help had sufficed

The cost of keeping an ambulant old person in a home for the aged is about £4 10*s* per week, but the minimum sum of £1 12*s* 6*d* (under review at present) of this is recoverable from the old-age pension It would therefore be economic to spend up to £2 10*s* per week on domiciliary services to enable the old person to stay at home Where the alternative is the more costly hospital bed, it would be economic to spend considerably more than this

A Choice of Priorities

The question we are faced with is that of translating into reality our ideals regarding the care of the elderly in their own homes The problem is not only one of reservations as to the cost but also the more serious difficulty of finding enough home helps of the right type, and it is not easy, when help is limited, to judge priorities accurately

How far are we justified in diluting the time given to those who need it badly so that those whose need is less may share in a service to which they consider themselves entitled? On the one hand we have long waiting-lists of old people who need home helps, and on the other the difficulty of recruiting home helps, a balance must be struck so that a reasonable, though perhaps inadequate, system of care can be provided There must be a good cadre of well-trained home helps, since, even under supervision, they have to work out of direct control but, owing to difficulties of recruitment, some less skilled workers must supplement the regulars The original conception of the home-help service has had to be changed, and conditions and standards of training and remuneration must be improved so that the work is given a better standing, for, as we have pointed out, much is needed from the home help beyond the capacity to clean a room The service can certainly no longer be haphazard in its organisation, nor can it hope to fulfil the needs of old people unless intelligent care and thought is given to each case and its work is supplemented by enlisting every possible source of help from relatives, friends, neighbours, and voluntary organisations

Since the number of aged is increasing and the younger people who must look after them are slowly getting fewer in proportion, there is a strong argument for the assumption by the medical officer of health of the overall supervision of the aged as a group The services and supervision which he is empowered to provide must match his awareness of the extent and nature of the need—in other words, it must be part of a social service and not merely a Domestic Help Scheme It is already realised that all the efforts which can be made on behalf of the aged by voluntary bodies will be required, and the function of these groups cannot be taken over by the local authority Nevertheless, preventive medicine in devising an intelligently conceived domiciliary service for the aged will have a chance of transforming their outlook in the years which must be lived on the debit side of life

The views expressed are personal and not necessarily those held by the Sheffield City Council

Food-poisoning

A new edition has appeared of the Ministry of Health's memorandum on food-poisoning[1] The only major change since the previous edition[2] is that provision is now made for the reporting of cases ascertained by medical officers of health besides those notified by other doctors

Vital Statistics for 1957

The Registrar General has issued provisional figures for England and Wales for 1957[3] The birth-rate (16 1 per 1000) was the highest since 1949, but the death-rate (11 5) was not much different from that in the previous two years The infant-mortality rate (23 0 per 1000 live births) and the stillbirth-rate (22 4 per 1000 live and still births) were the lowest ever recorded in this country

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[1] Food Poisoning Steps to be Taken in England and Wales by Medical Officers of Health in the Investigation and Control of Food Poisoning H M Stationery Office, 1958 Pp 15 1*s*

[2] See *Lancet*, 1949, i, 974

[3] The Registrar General's Weekly Return for England and Wales week ended Jan 18, 1958 H M Stationery Office Pp 20 1*s* 6*d*

Special Articles

CARE OF THE MONGOL BABY

The First Phase

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The birth of a mongol baby presents one of the most difficult and delicate management problems in family medical care Mongolism is, it is true, only one of the many forms of "congenital defect", and the parents' reaction involves no new or different quality What singles out this problem is, first, that it concerns mental defect, and, secondly, that if the presentation is vertex, the first look at the head and the face, before the whole baby is born, can reveal diagnosis and prognosis—the sadder because medicine cannot help

Mongol babies are not all the same, but they are similar, they share appearance, stature, colouring, a happy character, a love of music and rhythm, and the ability to give and to inspire deep affection While intelligence varies widely, and occasionally reaches the standard of the educationally subnormal, the range is as nothing beside the immense potentialities of the normal newborn babe, and full maturity falls short of independence in the complex of modern society

Parents of congenitally defective children can usually accept at birth such internal disease as involves the gut or the heart Anxiety there is, but compassion also, and the saving hopefulness that the doctor can generally give External defects are harder to bear, because the child will be perhaps crippled or unsightly, but if the parents are given honestly and without delay the whole picture of what can be done and what cannot, after their grief they usually adjust themselves and rise to the occasion Feelings of shame and guilt, or of retribution and punishment, are present in small degree, but where there is mental defect these feelings may well swamp compassion and substitute self-pity and a self-protective aggressiveness—understandable, forgivable, but making it hard for anyone outside to help

These attitudes are usually modified by the quality of the particular parents—strength of character, emotional stability, insight—and by their experience of life Intellectuality is, alas! a hindrance rather than a help The mother is bound after her pregnancy and delivery to be not her usual self, nor is she expected to acquire her normal emotional tone for six or eight weeks at least And no-one is likely to know really what hopes, joys, fears, or regrets have swayed her mind from the moment of conception, or whether the bonds of the family circle are such as will be strengthened or weakened by a family tragedy The community assumes that parents welcome the knowledge of a pregnancy, want babies, and love and cherish them from birth That some parents use contraceptives, successfully terminate pregnancies, or reject normal babies, is viewed with sympathy by society, which condemns infanticide and physical neglect, but recognises the instinct for rejection of parenthood in normal human nature

* * *

Faced with the certainty that the new baby is a mongol, what is the doctor to do? Although there is no way of altering the baby's condition, the doctor should work towards securing for the baby the care and protection which will allow him to develop to the limits of his capacity His needs in infancy are exactly the needs of the mentally normal baby physical care and satisfaction in an atmosphere of love and security To say that the mother at home and in her own family circle can provide these best, is to state an ideal It is not always the truth, and the ideal cannot always be achieved The mother and the father must be helped to accept the facts, helped to face them and their implications for the future, and helped to think out their plan for the care of the baby. The doctor must watch, so as to avoid, or at least lessen, the dangers to the family structure that arise while the parents are adjusting themselves to their experience. It is not the duty of the doctor, any more than it is the duty of the grandmother, to impose the solution. Nothing can alter the fact that the parents have a mongol baby. Whatever the fate of the baby, this fact will remain a fact for the rest of time, and the parents must make their plan with a sense of this perspective, leaving no place for regrets.

Once the diagnosis has been made, the possible lines of action are limited. The extremes are to keep the baby at home as a normal baby and to await developments, or to dismiss and reject him, to write him off as a "dead loss" and to find someone else to look after him—in a foster home, a nursery, or an institution. What is politely called euthanasia has no place in the care of the mongol baby and his family. Fostering, with a view to a later return home, or home care, with a view to admission to institution or residential school at some selected age, form intermediate compromises.

If the parents fail to notice that the baby is not normal (and this is usual even when parents include a doctor or a nurse) it falls to the lot of someone at some time to break the news. That person ought in the first instance to be a doctor, but whether he is family doctor, obstetrician, pædiatrician, or mental-health specialist depends upon who is available at the appropriate time, and is less important than the sort of person that he is. Let him be one who feels deeply about this problem, deeply enough even to pray before the interview and to weep afterwards. But the more deeply he feels, the more need is there for him to have thought deeply too. Whatever words are spoken, however many the talks, there are two moments in time to be bridged—the last in which the parents look with joy at their new baby and his future and the first when they know his tragedy in their hearts. The doctor who tells the parents that their baby is a mongol is performing a surgical operation without an anæsthetic. Only in the spirit induced by this sort of realisation should the doctor proceed with his hurtful and dangerous revelation. Upon his wisdom, upon his ability to see the situation as a whole, and upon the acceptability of his approach to the parents, may depend the future happiness and integrity of the affected family. That he imparts a bias of his own to the course of events is inevitable, but there is no place in all this for the doctor who always recommends the same solution, whether it be immediate separation or its opposite, or for the outpatient teaching session or a three minutes' chat in the doctor's surgery or the welfare clinic, nor for those to whom the consultation is no more than a rapid exercise in clinical diagnosis.

* * *

The parents should be encouraged to return for further talks at leisure, and in many cases a trained social worker or a sympathetic ward-sister, midwife, or health visitor can help. The list of things that the parents want to know varies little. Firstly, they need to believe the diagnosis and to accept the accomplished fact. "What will the child be like, will he live, how does it happen, why did it happen to us, can it or will it happen again, is there anything that we can do, is there anything that anyone can do?"

Acceptance and grieving form the first two stages of the healing process, and several expert opinions may be needed. Even then parents may appear not to accept the diagnosis. In some this is "putting a brave face on things", in others it is a dangerous delusion. The doctor who has made his point need not keep driving it home, and patients cannot be compelled to be cured of this or indeed of any delusion that does not lead to crime. Attempts to alter facts through quackery or spiritual healing under whatever banner are reasons more for pity than for interference.

A description of the life-history of the mongol baby and child is most important. Parents who lack direct experience of mental defect imagine what they do not know, and their own picture may be grotesque and terrifying. On the other hand, a visit to a home where there are many mongols is seldom wise. The suggestion to see some affected babies or children should be left to the parents to make, and tea with a high-grade case will show the best that can be hoped. About a quarter die in the first two years but many live on, especially when there is no complicating congenital disease. Resistance to simple infection is less than normal, but the parents should not be led to believe that their child will die young.

The ætiology of mongolism remains unknown. The great similarity between cases in different families, stocks and races, suggests that this is a human variant arising in between one and three of every thousand live births, commonest when the mother is over 40 years, but seen throughout the childbearing period. There is no known factor in the medical history or habits of the parents, and bad luck alone accounts for why this, which is a common risk to all humanity, should happen to one family rather than to another. Nothing in the parents' lives could produce it, nothing could have prevented it. Second cases do occur apart from twin births, and the parents must be so informed. The risk is not altered by the birth of a mongol, and is neither greater nor less at the next pregnancy. Nevertheless, with parents under 40 years the remark should be added that in real life second cases are exceptionally rare and the risk is well worth taking, especially when the mongol baby is the firstborn.

That there is no specific treatment must be admitted, but it is wrong to tell the parents that they can do nothing. Recent study of mentally defective children has shown the important part played in their lives by emotional disturbance. The emotional stability, the happiness and the general progress of the mongol baby is observably better when the family has accepted and loved the baby. This is no reflection on nursing care in foster homes and institutions, but simply means that the well-known fact that in the first five years home life is best for children applies to mongols as much as to their mentally normal siblings. When parents neither accept nor love the mongol, home care is not the best.

Certain other problems should be raised. The effect on the siblings of the addition of a mongol baby to the family has to be watched. The rest of the family usually takes the lead given by the parents, and if they adjust well to the situation little trouble results. From time to time the progress and behaviour of the siblings should be considered, and in some families the best interests of the normals may lead to a change of plan. This is the more likely if the mother gets into the habit of fostering her mongol at the expense of the siblings, and parents should be warned of the danger of the mother's neglecting her husband, her other children, or her home by concentrating too much on the mongol. It is wise for the parents to let near relations and close friends know that the baby is a mongol, that they have taken advice, and that the matter need not be referred to again'

* * *

The certainty of diagnosis that may follow the first look at the head of the part-delivered baby, referred to above, is responsible for the difficulty which surrounds the choice of time for revealing the fact to the parents There is room for difference of opinion and of practice If the baby is born at home, there is not the urgency that exists in hospital where the mother and baby normally go home on the tenth or the fourteenth day A routine method of handling is to be avoided, but on the whole I prefer to do no more than sow a seed of doubt in the parents' minds before they go home In this way the mother is given the chance to regain her emotional balance and to get really to know her baby I arrange to see them again at four or six weeks on the ground that the baby's general condition and progress is not absolutely satisfactory This conversation probably is wise, although at times it leads to a fuller revelation of the nature of the anxiety than was intended The parents must never be told positively that a mongol baby is normal, or confidence between doctor and patient is lost for ever Both parents must be seen at the second consultation, and at this or at the next, after a further one or two months, the full story should be told Unfortunately during these intervals a kind friend, neighbour, or relation, or another doctor or health visitor, may have alarmed the parents by some ill-advised remark, and it is wise for at least the medical and social workers to agree their plan

For the doctor to tell the father in the neonatal period with an injunction not to tell his wife is to put a dreadful strain on him, and reflects a singular idea of relations between husband and wife during their enjoyment of the new baby Often, however, the father is prepared to break the news to his wife and then to let the doctor explain the meaning of the diagnosis To tell the mother in the neonatal period before she has got to know her baby is again adding to the burden, unless the family situation is such that rejection of the baby seems likely to be the best solution When the parents have realised the diagnosis themselves, the decision is out of the doctor's hands One mother may utterly reject the baby in hospital and when the diagnosis is revealed in the first few days, she refuses to discuss it, seeming able to cut herself off successfully, though grieving privately Another, out of the fullness of her maternal spirit, cannot even for a moment consider a parting Such strong instinctive decisions are best left unchallenged

When the mother decides to keep the baby and to see how he gets on, she should be advised not to close her mind against his ever going away If he is very slow and limited the needs of the rest of the family may make it advisable, training and such schooling as is suitable may be possible only away from home, though this is less likely now that more occupation centres are opening Multiplication of instances is not the purpose of this article, each situation has its own characters and the best solution has to be worked out afresh each time The doctor can only help the parents to react well and try to persuade them that the birth of a mongol baby is not a defeat but a challenge to battle

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Medicine and the Law

An Unstable Piano

A SCHOOL music-teacher employed by a local education authority had her foot crushed by a piano while moving it in the course of her teaching duties at a special school for crippled children, carried on at the Ascot Orthopædic Hospital under sections 62 and 63 of the National Health Service Act, 1946

The education authority provided teachers and the hospital provided accommodation and equipment, including the piano in question It had originally been fitted with four one-inch-diameter brass castors at each corner and two wheels in the centre which made it easy to move from ward to veranda and back again Some time before the accident the two centre wheels had been taken off and it became difficult to move The school headmaster repeatedly asked the hospital to replace the wheels On the date of the accident two hospital employees replaced the brass castors by four 3-inch-diameter wheel-castors in the hospital workshop, and took it back to the ward for the music lesson While the teacher was moving it back to its proper place in the ward it tipped over and injured her

She brought an action both against her employers (the education authority) and against the hospital management committee Mr Justice Stable awarded her £1013 against the hospital and dismissed her claim against her employers The hospital committee appealed

Lord Justice JENKINS said that this piano had had a long and blameless if somewhat nomadic career until its centre of gravity was raised by substitution of wheel-type castors for the old brass ones, thus making it top-heavy It was highly significant that this accident happened on the very day of the alteration If that was the cause of the accident, was there any breach of the duty owed by the hospital to the teacher? For the hospital it was argued that though the standard of care they owed her was higher than that of the donor of a gift to a donee, it was not so high as that of a manufacturer of goods who made and distributed them for reward His Lordship did not agree that this was like a case where the work was done gratuitously It was true that the piano belonged to the hospital and was lent without any payment to the education authority, but it was lent as part of the reciprocal arrangement between these two public bodies who together fulfilled the aims of education and medical treatment, and the duty of the hospital committee was to take reasonable care to see that the piano when fitted with the new castors should be reasonably safe No-one who had heard this case could fail to appreciate that upright pianos were liable to tip over, and the higher their centre of gravity the greater the propensity to tip over That was something which the hospital employees using reasonable care ought to have known and guarded against, and because they had not done so the hospital committee were vicariously liable Their appeal must be dismissed

As to whether the education authority was liable, this was not a case in which the employers provided plant in the shape of pianos or delegated their provision These were simply pianos which the authority's employees were permitted to use, and it could not be said that when the piano owners caused new wheels to be put on they were altering plant on behalf of the education authority True, the headmaster had asked for new wheels to be put on, but the education authority was not in control of the situation when it was done The accident happened before the employers even knew that the new wheels had been put on They could not in those circumstances be held liable The claim against them must be dismissed and the hospital committee should pay all the costs involved

Lord Justice HODSON and Lord Justice MORRIS agreed

JOHNSON *v* BERKSHIRE COUNTY COUNCIL AND THE WINDSOR GROUP HOSPITAL MANAGEMENT COMMITTEE *Court of Appeal* (Jenkins Hodson and Morris *L.JJ*) Dec 5 1957 Counsel and solicitors —F Beney Q C, and John Perrett (Gamlen, Bowerman and Forward for Lovegrove & Durant Windsor), E S Fay, Q C, and P M Blomefield (K Wormald), Montague Berryman, Q C, and E W Eveleigh (Berrymans)

M M HILL
Barrister-at law

In England Now

A Running Commentary by Peripatetic Correspondents

"IT is just like a sort of outpatient department" said my learned colleague. The juvenile court was in session and we were observing from the rear. The longer I watched, the more I saw his point. There had been those dreary queues for a start, in a large dim hall complete down to the small wooden table in one corner serving warm tea. Even the stray coppers weren't out of place. The chief consultants were pretty obvious behind the Bench, and their juniors presented clinical problems to them in a competent manner; the conclusions were probably not much more didactic than those at most teaching hospitals. Once the three chiefs even withdrew for a private consultation on a problem case. Most cases were appropriately returned home for domiciliary care under the direction of the, as it were, court general practitioner—the probation officer. Some were declared fit and discharged, and a few, after some headshaking and study of specialist reports (including, happily, psychiatric opinions), were sent for special inpatient care at a specified place.

These parallels seemed for the most part happy ones; a therapeutic approach is making some inroads on our punitive judicial system. But there were differences too. The Press isn't admitted to our ward rounds yet, and the magistrate still has a very strict set of rules to follow. We haven't had these since Ancient Egyptian times. No, it's not for nothing that we talk colloquially of beaks "dispensing justice", but with due humility I would like to suggest that the legal eagles tear one more leaf from our book and initiate a series of carefully controlled trials. Where prognosis is so obscure, how can one have much confidence in the treatment?

* * *

In our industrial part of the world, one of the interesting sights of road travel are the chemical tank wagons, bearing in large red letters such exciting notices as DANGER, *HIGHLY INFLAMMABLE*, STRONG CORROSIVE. As one follows them it is interesting to revive one's rusty chemistry and think out what first-aid treatment would be needed if an accident occurred. But in fact their presence seems to have a good effect on road manners. It is striking to watch how the motorist who has been trying to pass everyone suddenly slows down when he reads the red letters which say DANGER. EXPLOSIVE.

* * *

She was rushed into hospital as an emergency and spent an hour and a half on the operating-table that same night. Thirty-six hours later she was asking me if there was anything new in the headlines of the morning paper. Then for a week or more she was very weak, and behaved like an old, old lady. She soon picked up again and discussed with great interest her curious adventures in the half-world where she had searched in vain for death's door. Today I took her an offering of *Penguins*, ranging from D. H. Lawrence to the Venerable Bede, and she seized on them with delight. She handed me in exchange an article she had just written about Irish nurses, and asked me to get it typed and sent off to a Dublin paper. I looked through it later. The writing was shaky but the style was as lively as ever. There was only one slip; meaning to mention her birthday in 1958 she had put, "This has been written on my 158th birthday." If bodily wear and tear had not taken such a toll, it would be hard to find any logical reason why she should not still be writing on that anniversary. Mentally she's still in her forties, for all that she's turned ninety-five.

* * *

Since the man from the Ministry fell through the seat of our Senior Lecturer's chair some time ago the University has been turning over in its mind the desirability of allowing us to purchase some new chairs. The green light came last month and we have all been breathlessly awaiting the arrival of our new Professorial Chair. Our Professor is not a man to throw away an opportunity of getting a decent seat for the first time in his medical career, and he has been happily studying the form in several highly coloured catalogues. On sordid financial grounds he was regretfully forced to leave out of consideration the 'Floating-Eez' (at the touch of a button instantly assumes any angle desired, the business man's dream, guaranteed for a lifetime), and the Executive's Chair (padded arm-rests and stout swivel mechanism, a solid job) seemed lacking in dignity. The Director's Chair (with foam-rubber seat and adjustable back, in blue, red, or green) was rather better, but our efficient administrator, who rules us in æsthetic matters, maintained that in her opinion the rest of the furnishings were not suited to admixture with primary colours. There was accordingly little choice in the matter, and our accommodating Professor was driven to turn his mind to those chairs which were obtainable in pastel shades.

Fortunately the *Chairman's Chair* (with foam-rubber seat, stout swivel mechanism, *and* patent adjustable tilting mechanism) came in grey or black, and this morning a grey one arrived in the hall, swathed in paper padding and secured at all points with string. We tiptoed cautiously round it, exploring the foam rubber, and examining the tilting mechanism, rather enviously we watched it borne away into the professorial sanctum. But mark the sequel.

It appears that our Professor was hospitably entertaining the Vice-Chancellor at morning tea when he conceived the injudicious notion of putting the Chairman's Chair through its paces for the benefit of his guest. The first tentative circuit of the stout swivel caused him to crack his patella viciously on a totally unexpected corner of his desk, and while expressing himself with some force on this occurrence he unwisely leant backwards, thereby bringing into play the patent adjustable tilting mechanism to such effect that the whole chair, complete with Professor, overbalanced backwards, causing him to strike his head a savage blow on the corner of the bookcase. The Vice-Chancellor's tea spilled all over the desk and overflowed on to his trousers, and our gallant administrator, roused by the clatter, tripped over the mat on the way to the rescue and joined the chaos on the floor.

The Chairman's Chair is now in the possession of our stolid Senior Lecturer, and our Professor has taken over a wooden affair which used to stand in the room where the cleaners make their tea.

* * *

George has just returned from an important conference on burns, and is full of the missionary spirit. How not to get burned is the answer to the problem, and we have all been deprived of our nighties and given 'Proban' pyjamas. Every fireplace has its own particular fireguard, and at last I think we are going to get central heating. So far so good.

Grandpa had a stroke about four years ago, and is unsteady on his pins. We have had no trouble with him about nighties, because he was "modernised" in this respect many years ago. But he says he hopes we won't get rid of the coal fire before he "goes"—in his more pessimistic moments he hopes he "goes" before we get rid of the coal fire. Although the new fireguard is an elegant affair tastefully decorated with ivy leaves, he regards it with distaste, and says it keeps the heat away.

Yesterday when I came in the fireguard was in front of the piano and Grandpa was standing on the hearthstone, swaying gently, holding his cold left hand well into the chimney. We hope George's next conference will teach him not only how to handle burns, but how to handle Grandpa.

* * *

He is a short, hardy, unwashed Eskimo. When he came to England he could not give up entirely his former way of life. He sleeps in as cold a room as possible, in a truncated bed with a mattress that would produce bedsores on a rhinoceros. It is the nearest approach to the sleeping bench in his igloo. He needs hardly any blankets, even in the middle of the winter. He seldom baths and when he does he dries himself with a minute square, of towelling, for cloth is almost unobtainable in the Arctic. He never uses soap. Unfortunately, I have never met him and no-one in the university seems to know him, but I am sure of his existence. I stayed for two nights in his room while attending a meeting during the vacation.

Letters to the Editor

ANTIBIOTIC PROPHYLAXIS

SIR,—I am perturbed by your annotation of Jan 4 I have not had the opportunity to read the papers on which it is based, but nevertheless I wish to make a few comments

No formal definition of prophylaxis is given, but your meaning may be thought to be implicit in the second sentence "More often than not, the belief that antibiotics will prevent bacterial infections is unjustified" This is a view with which there can be no quarrel if the word "infections" implies, as I believe it should, invasion of patients, after they have started antibiotic treatment, by bacteria new to them or at least absent from them at the time when the treatment began Theoretically, however, it is surely possible that such invasion might be by organisms sensitive to the drug being used, and thus infection would not become clinically manifest and so might be said, in a sense, to have been prevented Hence it might be maintained that the statement "To use antibiotics for clean operations with the object of escaping wound sepsis or respiratory complications is a vain hope" is logically indefensible even if one cannot commend the practice it condemns But what is a clean operation? And does not prophylaxis in this context refer not to pure aseptic cleanliness, since that is unattainable, but rather to the control of those ineradicable organisms which lurk subclinically, waiting the opportunity afforded by operative trauma to spread and multiply?

From the remark "Among patients undergoing operations (for) resection of the colon with anastomosis, postoperative complications were as common in those who received antibiotics as in those who did not" it might be thought legitimate to infer that modern methods of preoperative preparation of the bowel by appropriate sulphonamide or antibiotic drugs are ineffective, this is contrary, I believe, to the majority opinion Equally, from the remark that "the incidence of wound infections after appendicectomy for acute-suppurative and acute gangrenous appendicitis was not reduced by parenteral tetracycline therapy" it might be assumed that there is no place in even the severest forms of acute appendicitis for antibiotic treatment, this too I believe to be at least debatable The evidence cited from the work of Petersdorf et al [1] appears to be unbalanced, for example, "No benefit was derived from the chemotherapy, on the contrary, patients given antibiotics were more susceptible to pneumonia, cutaneous staphylococcal infections, and bacteræmia due to gram-negative bacilli", and again "Routine administration of antibiotics did not prevent infection but often resulted in the infecting organism being a highly resistant proteus or pseudomonas", these statements seem to me to savour of special pleading, even of propaganda If this is so it might appear that you have spoiled an excellent case by biased overstatement and so failed to carry conviction in the entirely laudable aim of reducing the indiscriminate use of antibiotics

Falkirk RONALD G HENDERSON

*** Mr Henderson seems to disregard a danger which has long caused us concern—namely, that the widespread use of antibiotics will, by suppressing susceptible organisms, enable resistant strains to become dominant in an individual or in a community Even when there appears to be a good case for the use of antibiotics in prophylaxis—as in operations on the bowel—there still seems to be some doubt whether clear evidence of benefit can be produced We are impressed by the reports to which Pulaski [2] refers, and by the findings of Petersdorf et al [1], and we do not think we overemphasised their implications —ED L

SIR,—Dr Warren Crowe (Jan 18) wishes to express his full agreement with your conclusion (Jan 4) that antibiotics should not be used to prevent sepsis, but he still recommends the use of sulphonamides as prophylaxis Are sulphonamides in effective dose not more toxic and hazardous than penicillin? The question is not what one uses as a prophylactic agent but whether "chemoprophylaxis" is beneficial and safe There are certain clinical conditions, such as rheumatic fever, disabling chronic bronchial infection, and valvular heart-disease in a patient undergoing dental extraction, where chemoprophylaxis and antibiotic prophylaxis have proved their value To withhold prophylaxis is, at times, more dangerous, but I would certainly reiterate that the antibiotics should not be used indiscriminately to prevent sepsis, especially in the conditions mentioned in your annotation

Victoria Hospital,
Accrington, Lancs
S S JHAVERI

SIR,—I was interested to read Dr Warren Crowe's letter (Jan 18) and to learn that he had been using sulphonamides prophylactically in the treatment of arthritis accompanied by focal sepsis He mentions that he has had some success with a new form of sulphonamide drug, and in this connection I thought it might be of interest to record my experiences with sulphaethylthiadiazole ('Sethadil')

Although recently introduced to this country, it has been in regular use since 1940, first on the Continent and then in the United States A long-acting sulphonamide, it is of great value in the treatment of lobar pneumonia, bronchopneumonia, and similar infections, as it has a potency and antibacterial spectrum which is almost identical with that of sulphadiazine or sulphafurazole [3]

I have used a great number of sulphonamides, but have always been conscious of the risk that they might lead to renal complications However, the risks of this with sethadil seem to be fairly small According to Frisk [4] and Terrell [5] only 5–10% of the drug appearing in the blood or urine is acetylated Terrell also states that the free drug has a solubility of 300 mg per 100 ml in urine as acid as pH 5 3–5 6

Three doses in twenty-four hours completely controls the majority of infections for which I prescribe it, and after the initial three doses a day I find that often only two doses daily is sufficient

In my hands sethadil is as efficacious as the best of the currently available sulphonamides, and to my mind it can be used with far less worry about harmful renal effects As it is not necessary to insist on the patients taking more than the normal amount of fluid per day, I find this drug particularly useful in cardiac cases and also in children where it is always difficult to give large amounts of fluids

Although this drug is rather more expensive than most sulphonamides, by using it in an increasing proportion of patients, some of whom I would normally have treated with very much more expensive antibiotic preparations, I am quite sure that I have effected an appreciable reduction in my prescribing costs

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[1] Petersdorf R G, Curtin J A Hoeprich P D, Peeler, R N, Bennett, I L *New Engl J Med* 1957, 257, 1001

[2] Pulaski E J *Practitioner*, 1957, 179, 465

[3] Rhodes R E, Bard, R C, McCaughan, J A *Antibiot Chemother* 1956, 7, 175

[4] Frisk, A R *Acta med scand* 1943, 103, suppl 142

[5] Terrell W, You, E M, Daeschner, W *Med Clin N Amer* 1957, 41, 546

London, N W 10 ERIC M SKLAR

PROBLEM FAMILIES

SIR,—Dr Scott reports in his "London survey" (Jan 25) that the incidence of problem families among the homeless is slightly more than four times as high as that ascertained by the public-health department among families living in their own homes In the television programme "Panorama" (Jan 6) the B B C showed briefly, but poignantly, the plight of families becoming homeless, and Lady Allen of Hurtwood writes [1] of her concern for the children who suffer with their parents in this way These reports are very disturbing

Dr Scott's survey demonstrates clearly that the "potential problem parent" does, by his own insufficiency, tend to become and remain homeless Careful consideration, however, of the many unavoidable reasons for which families become homeless points inescapably to the conclusion that the consequent suffering and degradation are sufficient to force even self-respecting families down into the "problem" group

The National Assistance Act, 1948, places a duty on the welfare department of the local authority to help any family whose homelessness can be said to be due to any circumstances which "could not reasonably have been foreseen"—fire, flood, and gale damage, for example, but not necessarily eviction in all its cruel and varied circumstance In contrast to the National Assistance Act, the Children Act, 1948, places a duty on the local authority, through the children's officer, never to refuse to receive into care any child destitute of shelter A cruel choice for parents separation and good material care for their child, or continuing a shared ordeal that only too often makes the child ill

Some brave and intelligent parents part temporarily with their children, and, competing with many other families in a similar plight, do find a new home, but, to quote Dr Scott again, "there seems to be a limit to the difficulties with which a stable but dull parent can compete, after which one further adversity will produce a complete breakdown in domestic management" Such parents give up their children and move into lodgings which, as childless people, they can find without difficulty Both may go out to work Why not? What hope have they of resuming normal home life? Probably they have another baby, and probably in consequence they are evicted from lodgings where they were accepted only because they were childless Meanwhile, the cost to national funds of maintaining their other children would be sufficient to pay the rent of an expensive family flat Some children thus grown up "in care" are placed in work with the help of the local authority Probably, by reason of parental deprivation, they are inadequate citizens. The cycle of problem families starts again

Some parents postpone the separation of their children from their mother by taking leave of each other The father goes into lodgings and has to pay for a landlady to look after him He has to pay also towards his wife and children's maintenance in either a homeless-family unit or short-stay accommodation The father must search for accommodation after the day's work and the mother during the day, taking with her in any weather whatever children they have, however young

It is at this point that I so often meet these families, referred from the casualty department, hungry and unwashed, the mother undeservedly drab, with broken shoes, and one or more of the children ill Usually with the children's illness the family's courage breaks, and they accept separation from their children for an indefinite time London is deservedly famous for its progressive and compassionate care of its children Dr Scott's survey shows again how wisely and how comprehensively London's children are known Nevertheless, in London and all up and down the country, these pitiful families move about without a plan, and by reason of just this aimless drifting they remain, for the ordinary citizen, out of sight Public concern, if informed, would surely give such support to the authorities which represent them that some way to surmount these almost insurmountable difficulties would be found

I must be one of very many people who would welcome such a public inquiry as Lady Allen suggests

Paddington Green Children's Hospital,
London, W 2 EILEEN SUMPTER

A FUNCTIONAL NECESSITY

SIR,—My letter of Jan 18 was concerned with the difficulties of securing the facts about consultant appointments and potential consultant vacancies I was not, therefore, as Lord Cottesloe suggests (Jan 25), "more concerned with attacking the Regional Board and its officers than attempting to deal with the extremely difficult problem of medical staffing" Indeed I have made considerable effort to get this problem fully ventilated, and I thought it helpful to your readers to quote the difficulty I had experienced in one regional-board area

I deliberately abbreviated my letter to you, Sir, and quoted only an extract from the written reply, because I am conscious of your need to economise in space I am, however, grateful to Lord Cottesloe for giving publicity to the questions I asked, but I must point out that he is in error in suggesting that he is quoting my request in full Nor would I wish to burden your readers with details of my efforts, commencing in 1956, to have this subject discussed in the duly appointed medical committee of the North West Metropolitan Regional Hospital Board

Without quoting the correspondence in full, perhaps I may be permitted to explain that I prefaced my nine questions with the words—"may the committee members please be furnished with the following information—or as much of it as can be made available —" Immediately following the questions my letter continued

> "I appreciate the fact that I am asking for a very large amount of information, some of which may not be readily available However, if we are to ensure proper staffing of our hospitals and also to solve the thorny senior registrar problem, I am quite sure that such details should be made available"

One is very glad to hear that a deputation visited the Ministry on Oct 16, 1957 Would it be too much to hope that the general purport of that deputation and its recommendations will be reported to the medical committee of the Board? Better still had the help and cooperation of that committee been sought first of all

I do most seriously submit that if regional boards do not make proper use of their medical advisory machinery it is virtually impossible for their professional staff to offer any concrete suggestions I feel sure that Lord Cottesloe will not be disappointed if he asks the help of his own medical committee, and his group medical advisory committees, in solving this otherwise intractable problem

Radlett, Herts R S MURLEY

SIR,—The whole consultant structure of the health service needs re-thinking Why is it not possible to have a pyramid of promotion in other hospitals similar to that in teaching hospitals? What is wanted is more jobs in the middle, not more jobs at the top It is not surprising that people fall off a ladder which has no rungs between the third and the sixth As long as the profession opposes the insertion of more rungs the senior registrars' present plight will remain

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[1] *Times*, Jan 25

In a system of more gradual promotion, although full consultant status would be reached at a much later stage of their careers, there would be a much larger number of jobs to which senior registrars could progress In this hierarchy people could be paid according to the position they occupy and possibly according to their skill and experience, so that there would be no need for separate merit awards

It is improbable that those who initiated the system of merit awards for consultants ever imagined that private consultant practice would continue to the extent it has Merit awards, if such a system is justified at all, should only be paid to full-time consultants Private practice brings its own merit awards to those who deserve them

A system of awards for years of experience would be more appropriate to general practice, where payment is by a fixed capitation-rate Few general practitioners engaged in N H S work can devote much time to private practice, so that the only way they can improve their position is by taking on more patients This is of doubtful advantage to both doctor and patient If a system of awards could be coupled with a reduction in the maximum permitted number of patients, more young doctors would be enabled to enter practice and fewer middle-aged doctors would be killing themselves

Hatfield, Herts KENNETH C HUTCHIN

SIR,—As a newly appointed senior registrar I have followed the recent correspondence with interest

I am working in pathology because this is the job I want to do I would far rather be an assistant pathologist than a principal in general practice, and by temperament and training I would be better employed in my chosen specialty A point that deserves wider recognition is that the career structure most appropriate to general medicine and surgery is not necessarily ideal for other branches, and should not be imposed merely for uniformity

The essential feature of such a grade as you advocate is that it must be from here that promotions to consultant are made Having this vital safeguard, I should regard such a post not as another obstacle but as a welcome milestone I am only sorry that those who claim to represent me do not share my views

TRAINEE PATHOLOGIST

A NEW FORM OF CHLORAL HYDRATE

SIR,—Chloral hydrate is still regarded as one of the safest and most satisfactory hypnotics, but its wider use has been limited by its disagreeable taste and odour, and the absence of any tablet presentation of the drug

Recently we have investigated a new product, dichloralphenazone ('Welldorm') This substance is a loose molecular complex of chloral hydrate and phenazone, which breaks down readily in the gastric juices to release chloral hydrate Dichloralphenazone is available in tablet form and, in effect, provides a readily acceptable means of administering chloral hydrate

We have given it as a hypnotic to a wide variety of medical and surgical cases (over a hundred) Its effects have been a satisfactory sleep with no hangover In particular the elderly patients in the sixth and seventh decade did better with it than with barbiturates

Its toxicity appears to be comparable to that of chloral hydrate No gastric or intestinal irritation has been observed from its use, and it appears to be very safe compared with the barbiturates

R A KING
I BIERER
P RICHMOND
London, W 1 A J WATSON

A THEORY OF NERVE DEAFNESS

SIR,—Dr Fisch (Jan 18) points out that we have used the term "presbyacusia" to denote any loss of high-tone sensitivity, without restricting its use to loss associated with ageing I apologise if this should produce confusion, and it is certainly etymologically wrong Whether or not non-conductive deafness in the young should be regarded as essentially different from old-age non-conductive deafness seems to be an open question, many workers—for example, Wever—seem to regard old-age deafness as being due to a series of minor injuries of various kinds, having cumulative effects with time They would make no theoretical distinction Perhaps our use might be excused, as one does sometimes talk about premature ageing

We are very grateful for any data provided by clinicians, and especially cases of neural damage which do not produce primarily high-tone loss In our paper (Jan 11) we did not suggest that the supposed increase in neural "noise" would be the *sole* cause of high-tone deafness, indeed, we cited three references giving evidence of partial sectioning of the nerve producing this effect We did suggest that loss of channel capacity, due either to increased "noise" or to loss of functional fibres, seems to give primarily high-tone loss On the other hand, we do submit that perhaps *recruitment* may be found only in the presence of noise, be this neural or external in origin Any data bearing on this would be most welcome

The finding of Dr Fisch that some lesions in the organ of Corti improve sensitivity for high tones is extremely interesting If the lesions were restricted to the low-tone end, then we should not be surprised to find low-tone loss, and primarily low frequency impairment may be produced experimentally in the normal ear by masking with a narrow band of low-frequency noise If the low-frequency end of the organ of Corti were entirely destroyed, then the normal residual neural noise from this region should be eliminated This could reduce the total noise-masking, and thus conceivably improve high-tone discrimination Could this be a possible explanation? Clearly, to test this, data are needed concerning the locus of the lesions

It seems worth adding that the change in the slope of the curves given by our experiment seem to indicate recruitment By including points representing lower background intensities more information about the slope of these curves can be obtained This differential intensity threshold technique might perhaps be used to estimate degree of recruitment where loudness balance cannot be used, and this might be clinically useful where both ears are impaired

Psychological Laboratory,
Cambridge R L GREGORY

SIR,—I have read with interest the article by Mr Gregory and Miss Wallace (Jan 11)

They say that peak clipping has been tried in nerve deafness but with only slight improvement, and suggest that it may be necessary to filter out those frequencies where impairment is greatest to reduce stimulation

Dr Harvey Fletcher in his book *Speech and Hearing in Communication* had advocated that in cases of high-note loss the frequency response of a hearing-aid should have a slope equal to one-third of that caused by the nerve-deafness factor, and this in most cases means greatly increasing the amplification in the high notes Hearing-aid manufacturers have successfully fitted aids in many thousands of cases of nerve deafness, using automatic volume compression and tone control along the lines recommended by Dr Harvey Fletcher In our experience it is essential, in those cases where the audiogram shows little loss in the low frequencies, to cut out these low frequencies below about 1000 c.p s almost entirely This produces in many cases a striking increase in tolerance and intelligibility

There is a school of thought that believes that distortion may be introduced by high-frequency sound and that this may vitiate the improvement of the hearing given by the lower frequencies

In some of the current hearing-aids manufacturers have fitted a "high-note cut" to take care of this factor, if it exists Experience indicates that while this switch is helpful in reducing rubbing noise it has not so far been possible to detect any improvement in hearing or comfort following its use It may be that the factors of stimulation and distortion arise above the highest effective frequency of the hearing-aid—about 3500 c.p s

I think we may fairly claim to be able to help 90% of the nerve-deafness cases referred to us, but I feel that we are going to require much more information before we can help the remaining 10% if, in fact, they will ever be helped at all by hearing-aids

Hearing Aid Manufacturers Association Ltd.,
Hastings House, Norfolk Street,
London, W C.2

A EDWIN STEVENS
President

ENZYME TESTS FOR GLUCOSE

SIR,—The 'Clinistix' test has recently[1] been found to be highly specific for glucose in urine, none of a number of other sugars, when freed from glucose, giving a positive result at concentrations below 20%

The first comprehensive investigation[2] of the specificity of glucose oxidase (notatin) showed that modifications to C6 of the glucose molecule reduced the rate of oxidation to 2% or less of that of glucose Within the past year 2-deoxyglucose has been reported[3] to be a fairly good substrate for this enzyme, Sols has also demonstrated that glucosamine is slowly oxidised at pH 8 0 Another substrate, which is oxidised at about the same rate as 2-deoxyglucose is glucosone (2-oxo- or 2-hydroxy-glucose)

Although glucosone and 2-deoxyglucose react readily with clinistix and "Testape" under the conditions employed in urine testing there is no evidence that either sugar ever appears in urine 2-Deoxyglucose has not, to my knowledge, been reported as a natural product, the possible biological role of glucosone as a metabolic product of certain moulds, and as an intermediate in sugar interconversions, has been reviewed recently[4]

Both sugars are, however, being used increasingly in metabolic studies, and the limitation of manometric and colorimetric glucose assay using glucose oxidase should be kept in mind

Department of Biochemistry,
St Salvator's College, St. Andrews

STEPHEN BAYNE

SURGERY OR RADIUM FOR CANCER?

SIR,—We write to refute the suggestion made by Dr Lederman and his colleagues (Jan 18) that we in Birmingham wish to revive the old conflict between radiotherapy and surgery In the United Birmingham Hospitals patients with carcinoma of the cervix are seen at clinics at which both radiotherapy and gynæcology are represented Furthermore, many gynæcologists working in the area have actively participated in the formation of our treatment pattern

There may be little to choose between the results of radiotherapy alone, surgery alone, or the judicious combination of both methods when comparable series of clinically and technically operable cases are reviewed We agree that radiotherapy is the treatment of choice in all stage-2 cases where the parametrium is obviously involved with growth, in addition to stage-3 and stage-4 cases In many of the remaining stage-1 and stage-2 cases with gross obesity or other serious medical contra-indications, radiotherapy is clearly preferable In the residual group (stage 1 and stage 2) the lower morbidity from irradiation treatment must be weighed against the possible advantages which operation affords of the dissection of pelvic nodes and concealment of the diagnosis[1 2]

United Birmingham Hospitals

H C MCLAREN
P B KUNKLER,
A L T EASTON
J A H WATERHOUSE

MANIPULATION FOR BACKACHE

SIR,—Knowing how successful manipulation can be, I admire Mr Bremner's efforts (Jan 4) Considering his cases were not chosen according to any definite diagnosis, his 10% success was good If a careful history of the onset of pain had been taken and manipulation had been carried out on those patients who had a sudden onset, the 10% might easily have risen to 50%

I do not agree with his using an anæsthetic, as, without the cooperation of the patient and a re-examination after each manœuvre, it is difficult, if not impossible, to tell whether an improvement has been obtained

Mr Thomas's reason (Jan 25) for manipulation shocks me To manipulate the spine as a "placebo", I hope will be deprecated by all his orthopædic colleagues

Mr Thomas mentions that he has never seen at operation a disc protrusion that could be reduced by manipulation That, of course, is as it should be Operation should be carried out only when the protrusion is irreducible by manipulation or traction, or if epidural local anæsthesia fails to bring relief

London, W 1

R BARBOR.

SIR,—Mr Thomas (Jan 25) has asked that very awkward question "What precisely do you attempt when you manipulate?" I agree with him that the glib answer about breaking down adhesions is improbable in this instance Personally I try to separate the joint surfaces to restore "joint play", and, if I am lucky, I break the vicious circle of pain—spasm—pain Treatment by rest, support, or the injection of a local anæsthetic may achieve the same result, but I have the "clinical impression" that manipulation is more effective

Is Mr Thomas convinced that the relief of pain which can follow manipulation of a hip is due to the breaking of adhesions?

London, W 1

W HARGRAVE-WILSON

SIR,—It has been said that there is no useful research without hypothesis Equally, no progress can be made unless one is prepared to revise the theoretical basis if the hypothesis does not fit the observed facts Nowhere does this seem more applicable at present than the prolapsed disc

The facts of the case appear to me that the disease commonly called prolapsed disc begins suddenly when the erector spinæ muscles are in tension and the spine is curved both forwards and laterally—for example, when the patient, with a bent back and straight legs, moves some heavy object (such as a shovelful of coal *or a* trunk) and passes it to one side

Another significant fact is that scores of unrecognised manipulators are making a laughing-stock of those orthopædic surgeons who believe in six weeks' rest or plaster jackets as a first ploy for conditions which lay manipulators, in spite of

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[1] Adams E C, Burkhart C E, Free A H *Science* 1957 125 1082
[2] Keilin D Hartree E F *Biochem J* 1948 42, 221 1952 50 331
[3] Sols A, de la Fuente G *Biochim biophys Acta* 1957, 24 206 McComb, R. B Yushok W D Batt, W G *J Franklin Inst* 1957, 263 161
[4] Bayne, S., Fewster, J A. *Advanc carbohyd Chem* 1956, 11, 43

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[1] Bonney V *J Obstet Gynæc, Brit Emp* 1941, 48, 421
[2] Currie D *ibid* 1958, 64, 871

little medical knowledge and no radiographic control, can cure in a matter of minutes—using " cure " in the sense that the patient's complaint of pain and disability is removed completely

In the simple manipulation which appears to be used by some of these operators, and which I was shown by an orthopædic surgeon two years ago, one rotates the spine by gently persuading the bended knee down to the floor or bed on the opposite side, while the patient is lying relaxed, face upwards In many cases this produces an audible crack, similar in quality to the noise emitted by a forty-plus doing a knees-bend, suggesting tense tendon or muscle slipping over a bony prominence I do not see how this noise can be produced by a protrusion and restoration of the intervertebral disc This noise is accompanied by a sudden relaxation of tension in whatever muscle is being stretched (presumably the erector spinæ group), which can be felt quite distinctly with the guiding hand This is followed immediately by improved mobility and decrease in pain in most cases

Putting these two facts together, I would therefore suggest that the primary condition in a so-called " slipped disc " is a displacement of a muscle bundle or tendon in the erector spinæ, which, because of its displacement and discomfort, goes into spasm This spasm may result in the nearby vertebræ being pulled tightly together and thus mechanically producing disc protrusion I suggest that if this disc protrusion involves irreversible trauma to its retaining ligaments, then the protrusion can become permanent and can indeed be the chief source of further muscle spasm and disability—irreducible by manipulation and requiring spinal support or operation or both

By means of this simple manipulation (to be done afterwards as exercise by the patient along with the more usual hyperextension exercises), I find that my rate for referral to hospital of these unfortunate patients is reduced to about a tenth

Perhaps I may quote a typical case illustrating these points

A commercial traveller, aged 51, was driving one day to Glasgow and missed his footing when getting out of the car He felt the usual knife-like stab in the back and found getting about extremely painful and difficult At one of our larger teaching hospitals he was very thoroughly examined and investigated, but no very concrete effort at therapy was made, and, after spending all day in various departments of the hospital, he decided to come home After an agonising night, he came to my surgery, where, by this simple manipulation, he was greatly relieved, his only comment was " Why didn't somebody do that in Glasgow ? " He has had only minor trouble since, from slight recurrences, which he has been able to control and manage himself along the lines indicated

I strongly support, therefore, those who urge early manipulation for " slipped disc ", and hope that those in a position to do so will be able soon to put this on a sound theoretical basis

Workington, Cumberland R N R GRANT

TREATMENT OF MYXŒDEMA

SIR,—We were much interested in the article by Dr Gibson (Jan 18) on the control of the treatment of myxœdema by electrocardiography His statement that only patients " with a significantly lowered basal metabolic rate (B M R) are included " is however a little puzzling, since three of his patients, nos 3, 6, and 7, had B M R s of −6%, −3%, and −11% respectively

Dr Gibson does not tell us the standards or method used for determining the B M R , and we should be much interested to have this information Robertson and Reid [1] have shown that when the standards of Aub and DuBois [2] are used, the range of normal variation in Britain is 0 to −20%, and Robertson (personal communication) accepts as normal a variation of +15% to −15% for the British standards of Robertson and Reid [1]

Dr Gibson gives detailed information about two of these patients (nos 3 and 6) Both of these had undergone thyroidectomy In case 6, the B M R was found to be −3% seventy days after a *complete* thyroidectomy Means [3] says that complete athyreosis develops in about eighty days after acute withdrawal of thyroid hormone It is therefore rather surprising that this patient's B M R was as high as the value given by Dr Gibson

Case 3 had a subtotal thyroidectomy The clinical findings, apart from tiredness, do not suggest hypothyroidism, the B M R was −6% and the serum-cholesterol 235 mg per 100 ml The only clear support for the diagnosis in this case appears to be the electrocardiographic changes, presumed to be due to thyroid therapy These changes are of limited diagnostic use, Means [4] found that 7 out of 24 athyreotic patients retained their T-wave abnormality after specific treatment

Department of Chemical Pathology,
West London Hospital, London, W 6

I J L GOLDBERG
M J SEAMAN

SYRINGES CLEAN OR STERILE ?

SIR,—Dr Morton (Jan 18) draws attention to the danger of a mass-inoculation technique in which one syringe is employed to inoculate many different people using a separate sterile needle for each patient It would be interesting to know whether the Medical Research Council is considering re-writing its official memorandum [5] which advocated this type of technique when mass inoculations have to be made, because most doctors who are giving subcutaneous and intramuscular inoculations ensure that the needle is not in a vein by pulling back the piston of the syringe after the needle has been inserted into the tissues It is curious that although nearly everyone is taught to do this it is not mentioned by the M R C and very few textbooks describe the technique

I have now read the leaflets issued with the poliomyelitis vaccine made by the Connaught Laboratories of Canada and Glaxo Laboratories and Messrs Burroughs, Wellcome of England The first two makers state that the vaccine should be given by intramuscular injections and the last intramuscularly or subcutaneously The Connaught Laboratories write " to avoid possible intravenous injection, pull back the plunger to make certain that no blood is withdrawn and then slowly inject the desired dose " This habit of preventing an intravenous injection, which I think any good doctor develops, and the use of the intramuscular route which Salaman et al [6] showed was liable to transmit virus hepatitis, indicate how unsafe a mass-inoculation technique, like those advocated by the M R C , could be The method of oil sterilisation [7] [8] would be very much safer as sterile syringes and needles are easily provided for every patient Very many children and some adults are now to receive poliomyelitis-vaccine inoculations, and I hope that a sterile syringe as well as a sterile needle will be provided for each patient

Children s Hospital,
Birmingham, 16

K B ROGERS,
Clinical Pathologist

SIR,—I am grateful to your correspondents for drawing my attention to the mistake in my letter of Jan 18 should have said that the syringes I described are sterilised in a hot-air oven

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[1] Robertson, J D , Reid, D D *Lancet*, 1952 i, 940
[2] Aub, J C., DuBois, E F *Arch intern Med*, 1917, 19, 823
[3] Means, J H The Thyroid and its Diseases Philadelphia, 1937, p 20
[4] Means, J H *ibid* p 249
[5] Medical Research Council war memorandum no 15 The sterilisation use and care of syringes, p 14 H M Stationery Office Reprinted 1954
[6] Salaman, M H , King, A J , Williams, D I , Nicol, C. S *Lancet*, 194 ii, 7
[7] Rogers K B *ibid* 1946, ii, 87
[8] Flemming A , Ogilvie, A C. *Brit med J* 1951, , 543

A local colleague, who uses similar syringe equipment, bought a second-hand electric oven, with a thermostat which maintains the temperature at 160°C, for about £12 This makes the cost of this technique of sterilisation comparable to the less efficient methods using water sterilisers

London, S.E.26 R N JACKSON

SPUTUM IN CHRONIC BRONCHITIS

SIR,—I was most interested to read the papers on this subject by Dr Brumfitt and his colleagues (Dec 28 and Jan 18), and it is gratifying to learn that conclusions based on sputum cultures are in general confirmed by their more elegant bronchoscopic swabbing technique I think, however, that two points require comment

The first concerns the site of infection in "bronchitis" In spite of the name, most of the inflammation, and presumably therefore the infection, is situated in the bronchioli and smallest bronchi, into which no swab can possibly penetrate[1] Bronchial swabbing, in the absence of infection of the larger bronchi, will only detect organisms deposited at the site by the passage over it of infected bronchiolar secretions, and consequently the recovery-rate of pathogens by this technique may well be *lower* than the actual incidence of these organisms in the bronchioles

Secondly, and more important from the practical standpoint, I feel that some qualification is required for Dr Brumfitt and Dr Willoughby's statement that "... the presence of pus was a poor guide to the presence of infective lesions of the bronchi" Presumably "infective lesions of the bronchi" in this context is synonymous with the presence of pathogens in the sputum This, however, is extremely variable from specimen to specimen in the individual patient, even when pus is present, and a true conclusion as to the pathogenic flora of any patient's sputum can only be drawn from examination of many specimens[2] Dr Brumfitt and his colleagues apparently obtained their results from the study of single specimens, and in these circumstances I would agree that the presence of pus does not necessarily indicate the presence of a pathogen. The correlation is much closer, however, if multiple specimens are examined, and our experience has been that in these circumstances the purulence of the sputum provides an excellent index of the presence of pathogens

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Brompton London S W3 J ROBERT MAY

SUBURBAN NEUROSIS UP TO DATE

SIR,—In your leading article of Jan 18 you cite the results of a recent survey illustrating the much higher incidence of psychoneurotic illness among the rehoused population of a newly developed "out-county" housing estate to the north of London, compared with the "expected estate figure on a national basis" obtained by the Social Survey of Sickness

In discussing this higher incidence you point out that rehousing on such estates is partly determined by medical certification, but it can account for only a small part of the excessive neurotic illness encountered From this it is deduced that the determining factor is the absence of social amenities and the degree of social isolation engendered thereby It is true that many housing estates in this country, private as well as municipal, are without adequate social amenities, and many rehoused families on municipal estates must indeed find it difficult to accommodate themselves to the new and unfamiliar surroundings, so different from the more sociable atmosphere of their former environment. In the process of adaptation, casualties undoubtedly occur

It should be remembered, however, that a rehoused population on a municipal housing estate is a highly selected population. The criteria of selection may vary in detail with different authorities, but, in general, priority is given to families who are either without accommodation of their own or are living under socially or hygienically undesirable conditions It is among this section of the community, which is least successful in obtaining decent housing conditions by its own efforts, that one would expect a higher incidence of and tendency to psychoneurosis than among the community at large. I consider that this selective factor is important—no less perhaps than that of the paucity of social facilities on the estates to which these people have been moved

It would be interesting to compare the incidence of psychoneurosis among the population of municipal estates on the one hand and of comparable private-enterprise estates on the other There might well be a significant difference

Health Department,
Colchester, Essex. R. E BARRETT.

DEATH FROM POSTMATURITY OR INDUCTION OF LABOUR?

SIR,—Mr Gibberd (Jan 11) accepts the dangers of postmaturity but wishes to convince us that the dangers of induction of labour are of the same order I should like to comment respectfully on two points in his article which I find unconvincing

If I understand his figures correctly, 1219 out of 8503 women (14 3%) at Queen Charlotte's Hospital reached forty-two weeks' gestation undelivered He therefore suggests that if forty-two weeks is taken as a reasonable "deadline", it would be necessary to induce labour in this number (1219) in order to avoid the hazards of postmaturity But he must surely agree that the label "forty-two weeks" in the hospital records often fails to stand scrutiny In a similar group of women reckoned overdue by the usual calculations, McKeown and Gibson[1] had to reject 172 out of 247 because of uncertainty concerning dates, bleeding in the early months, and a long or irregular cycle Further, it is generally believed that the multigravida is notably less liable to fœtal loss from postmaturity, though she is equally liable to be overdue Thus I think that many a clinician might induce labour in only a quarter of the total number suggested by Mr Gibberd, but out of that quarter he might hope to salvage (say) three-quarters of the possible loss from postmaturity

My second point of disagreement concerns that small hard core of primigravidæ who have been correctly assessed as postmature but, when induction has been tried, refuse stubbornly to budge Whether it be failure to start or an inert or disordered action after starting, I believe forty-eight hours to be the maximum safe period to allow following surgical induction in confirmed postmaturity I found this to be true in a previous series[2] and the 4 cases of stillbirth quoted in Mr Gibberd's article seem to emphasise this

No-one would dispute his point that the perfectly safe method of induction has not yet been described One could wish, too, to have some cast-iron test (e g, by paracentesis) to confirm one's clinical impression of postmaturity But even without these things, I think that better results can be obtained than those which follow a policy of strict non-interference, provided the clinician adopts a policy of selection and not routine induction, and provided he is prepared to undertake a number of cæsarean sections in the fœtal interest in a group with a high fœtal risk

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[1] Reid L. M *Lancet* 1954 i, 275
[2] May J R. *ibid* 1954 ii 839

[1] McKeown, T Gibson, J R. *Brit med J* 1952 i, 938
[2] Parker, R. B *J Obstet Gynæc, Brit Emp* 1957, 64, 94

Birmingham R B PARKER

SIR,—In discussing the management of established postmaturity Mr Gibberd has made a critical analysis of surgical induction of labour as a method of dealing with this undoubted problem

In table II of his article 4 stillbirths are recorded in 68 surgical inductions for postmaturity at Queen Charlotte's Hospital From these figures he concludes that induction is too dangerous to use in an attempt to reduce stillbirths due to postmaturity That this hazard need not be so great is, I think, shown by the accompanying table which I have compiled for surgical inductions of labour carried out at this hospital during the 3-year period 1955–57 when there were 1882 deliveries of viable infants The indication in each case was postmaturity alone

INDUCTION OF LABOUR BY ARTIFICIAL RUPTURE OF THE MEMBRANES FOR POSTMATURITY WITHOUT OTHER ABNORMALITY

Completed weeks of pregnancy	41	42	43	44 or more	Total
No of inductions	3	35	8	1	47
No of cæsarean sections after failure of induction	1	3	1	1	6
No of stillbirths	0	0	0	0	0

There were no stillbirths in these 47 inductions, but cæsarean section was resorted to more frequently than in Mr Gibberd's series This is presumably justifiable in view of his comments on the 4 stillbirths in his series

During the same period 1955–57 there were 5 stillbirths in this hospital attributed to postmaturity alone in patients who were not induced (fœtal loss 0 26%) These occurred despite the general policy to induce labour soon after 42 weeks where postmaturity seemed established It appears that induction with early resort to cæsarean section if the induction is unsuccessful can be safely used to save more babies but is not the complete answer to the problem

I wish to thank Mr Leslie Williams for permission to include in this letter the figures used above

St Mary's Hospital,
London, W 2 P S WATSON

UNUSUAL URINE PROTEIN IN MYELOMATOSIS

SIR,—We were interested in Mr Cummings' letter of Sept 21

Fifteen cases of myelomatosis were studied by paper electrophoresis of serum at the 2nd Clinic of Internal Medicine of Athens University (under the direction of Prof A Gouttas) In two cases, two pathological fractions were found instead of one

In the first case no pathological fractions were found in urine In the second case the only pathological fraction in urine corresponded to the slower and smaller pathological fraction of the serum

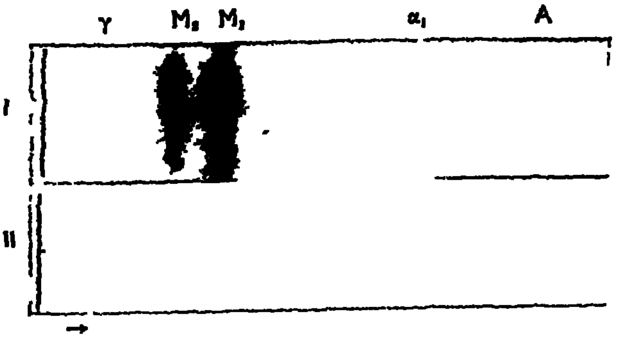

Fig 1—First case Electrophoretic patterns of serum (I) and urine (II). Buffer: veronal, pH 8·6. Paper Whatman no 1 Stain: Bromophenol blue.

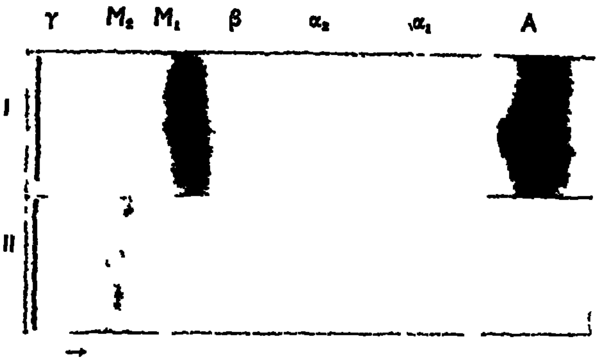

Fig 2—Second case Electrophoretic patterns of serum (I) and urine (II)

The existence in the serum of two pathological fractions, in some cases, may perhaps explain the presence in the urine of two pathological fractions It is strange that, in our two cases, electrophoresis of urine did not show the existence of the two pathological fractions

The pathological serum fraction in Mr Cummings' case may possibly have consisted of two fractions in close contact, which could be separated by the urine electrophoresis Perhaps electrophoresis of a highly diluted specimen of serum could demonstrate the existence of two fractions

Hippocration Hospital,
Athens, Greece HIPP TSEVRENIS
BYRON G SAMIOS

WHERE DOES MEDICINE FIT IN ?

SIR,—Dr Manning[1] says that "the ever-increasing insecurity and instability of our world brings us, as doctors, face to face with people cracking and creaking under the strain"

As "the true answer" to this situation he suggests

> "It is only by putting man in his right place—by viewing him in perspective—that we shall realise just how small and insignificant his troubles are We have somehow to learn that we are not the centre of the Universe, that we are not different from other forms of life, and that we have not even full conscious control of our minds We have existed for only a very short time in a very small part of the Universe Though we happen to be the leading current form of life on our planet we are neither the biggest nor the most long-lived, and there is nothing except our pride to suggest that we are the ultimate in Evolution "

So this is what we are to tell those of our generation who are cracking under the strain of the insecurity and instability of Life "Fear not You are of no importance We live on a mere speck of the Universe We have been here a very short time compared with the amœbæ The elephants are far bigger than we are and live longer Please do not take yourself too seriously"

Is this sort of thing going to ease the pain of people racked by fears? Is it even rational? Is the significance of human life to be measured by the space and time in which it has been lived? If human life is the highest point in evolution, how can it have any but the shortest history?

To say that human life does not differ from any other form of life is a mere gratuitous pronouncement If we take into consideration the extent to which humans have outstripped other species, we are compelled (apart from religious faith) at least to reserve judgment on a question such as this If the Earth is but a tiny part of the Universe, is there any evidence whatever of life like ours in any other part of the Universe? If there is life like ours elsewhere, how does this make ours any less significant? Even if this sort of thinking were unassailable, how can it be considered helpful to a fear-ridden generation?

I quote the well-known statement of Jung

> "Among all my patients in the end half of life, that is to say over 35, there has not been one whose problem in the last resort was not one of finding a religious outlook on life It is safe to say that every one of

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[1] *Lancet*, 1957, ii, 1274

them fell because he had lost that which the living religions of every age have given to their followers."

Would people haunted by fear and insecurity in the present age not be likely to benefit more from the Christian faith than from the "cosmology" suggested by Dr Manning? Surely, the claims of Christian teaching should be eagerly appraised. But Dr Manning does not give a moment's consideration to religious faith. He says that our generation has thrown it overboard and prescribes for the world's ills as if religion did not exist.

If Dr Manning and those who think like him have abandoned the Christian view of life, I hope that before doing so they gave to its credentials the consideration they demand. However, if after doing so they fail to accept the Christian faith, they should remember that there are very many who are deeply convinced that it represents the truth.

Ballina,
Co Mayo

G E HEWSON

EARLY ADMISSION TO HOSPITAL OF MENTALLY DEFECTIVE BABIES

SIR,—Miss Adams' views[1] about the care of the mongol child are of interest, but we must remember that the life-span of a mongol can extend up to 72 years.

Formerly, I thought that the mongol child's best interests in early childhood were secured by keeping him at home. It is hard to realise that the infant mongol, with his healthy appearance and almost normal early development, will so deteriorate physically and mentally that at the age of 10 and afterwards he will have a mental age of 3–4. The decision must be made on the exclusive fact that the infant mongol can never become an independent person, mentally or economically. The female mongol is better adapted to home care than the male, and exceptions may be made to the general rule of institutional care in her case. As long as the home is intact all is well, but inevitably the parents die. At this late date in life custodial care in some form must be provided, involving a difficult adjustment period to a mode of life which she is not adapted to but which must be endured henceforth. Her greatest task is coping with her memories, which in the mongol are maintained at a high level.

The initial decision about the care of the mongol should not be influenced by emotional factors, theories, or personal prejudices. The mongol infant should not be used to satisfy a temporary intense maternal instinct provoked by the birth of a child. My opinion is that the normal-minded mother can use her reason if she unfortunately gives birth to a mongol child. She should not permit the development of a selfish frustration. Her husband should not be censured because he arranges for his mentally deficient baby to be admitted to an institution which can give him, as he develops, a happiness, a state of wellbeing, and a life with opportunities and an environment which no amount of wealth can give.

One of the major advantages which the mongol has in an institution is that he is living in an environment of equality of abilities, he has physical freedom and competitive opportunities in sports where handicaps are equalised, and is not frustrated by exhibitions of physical dexterity and mental normality. Individual and small-team competitive spirit is at a high level of enthusiasm. In a good institution he will not lose his family membership, because a competent social-service worker maintains and promotes family membership. This type of function by a social-service system is in direct contrast to the role which Miss Adams plays in the care of the mongol. I do not feel she is contributing anything constructive by increasing the frustration of the mother when she criticises the obstetrician and pædiatrician and condemns the husband for acting on the wisdom and long-term outlook of his competent advisers.

For over fifteen years I have treated in an endocrine clinic young mongol children from a hospital for the mentally retarded—but not on the premise that a hormonal deficiency is a primary ætiological factor. Thyroid is administered in the presence of clinical hypothyroidism, I find the mongol child more prone than the normal to the hypothyroid state.

I gave stilbœstrol to the males with sexual disturbances, and in a few patients who were strong-willed and would flee from protective observation, I insisted on protective institutional care.

Later I began early stilbœstrol therapy to inhibit gonad development. This prevented trouble when the patient found that the heavy dose of stilbœstrol required to suppress erections also produced breast development and deep pigmentation of the areola.

When I assumed my duties as consulting endocrinologist at the hospital for the mentally retarded in late 1955, I had my first opportunity of observing and studying 50 mongols whose ages ranged from infancy to 72 years, and some 25 patients who were receiving endocrine therapy at home. I had little doubt that the survey of 75 mongols showed that the endocrine-treated mongol from the institution was the happiest and best-established individual, because socially, mentally, physically, and occupationally he was the most advanced and accomplished, this applied to both sexes.

Philadelphia,
Pennsylvania.

CHARLES W DUNN

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[1] Lancet, 1957, ii, 950.

CONGENITAL GALACTOSÆMIA AND MENTAL HEALTH

SIR,—Current textbooks of medicine and pædiatrics discuss congenital galactosæmia only briefly.[1 2] The incidence of congenital galactosæmia has not been established for lack of simple screening methods, but there is reason to suspect that the disease is not as rare as hitherto assumed. Awareness of the disease is essential for early diagnosis and treatment so that serious consequences may be prevented. Two illustrative cases are here reported.

A white boy, aged 13 weeks, was admitted to the Children's Hospital of Los Angeles with a diagnosis of galactosæmia made in another hospital by history and by the presence of reducing substance and albumin in the urine. At the age of 14 days the formula had been changed to one containing no milk. Subsequently, the infant ate well and gained steadily. The original diagnosis was confirmed by a galactose-tolerance test and by assay of red blood-cells for PGal uridyl transferase,[3] by newly developed specific methods.[4–6]

An older brother had been in an institution for feeble-minded children for several years. His I.Q. at 12 years of age was estimated at 11, and he could neither talk nor understand words addressed to him. Galactosæmia had never been suspected, though he had been examined at several clinics. His feeble-mindedness had been ascribed to erythroblastosis. It was known that he had bilateral cataracts. Blood was made available for study through the cooperation of the staff of the institution (Dixon State School, Dixon, Ill.), and we are especially grateful to Dr Abraham Gelperin. It revealed a striking defect of PGal uridyl transferase. The galactose-tolerance curve was also abnormal.

It seems highly probable that similar cases of unsuspected galactosæmia are present in mental institutions. Dr Robert Cooke, of Johns Hopkins University, has found three cases of galactosæmia in training-camps for retarded children (personal communication).

To clarify the incidence of the disease and to detect unknown cases for possible therapeutic benefit to them and certainly to their newborn siblings, large-scale screening seems advisable in institutions for mentally retarded children. The clinical indications for further screening might be based on the following

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[1] Cecil, R. L., Loeb, R. F. Textbook of Medicine. Philadelphia, 1955.
[2] Holt, L. E., McIntosh, R. Pediatrics. New York, 1953.
[3] Kalckar, H. M., Anderson, E. P., Isselbacher, K. J. *Biochim. biophys. Acta*, 1956, 20, 262.
[4] Anderson, E. P., Kalckar, H. M., Kurahashi, K., Isselbacher, K. J. *J. Lab. clin. Med.* 1957, 50, 469.
[5] Maxwell, E. S., Kalckar, H. M., Bynum, E. *ibid.* p. 478.
[6] Schwarz, V., Holzel, A., Komrower, G. M. *Lancet*, Jan. 4, 1958, p. 24.

(1) A family history of galactosæmia
(2) *A history of unexplained neonatal jaundice*
(3) Lenticular cataracts
(4) Enlarged liver
(5) Reducing substance in the urine which gives negative test on glucose test paper *

Confirmatory laboratory tests, such as the PGal uridyl transferase assay, could be used in suspicious cases Classical methods for identification of urinary reducing substances by chemical or chromatographic methods, and the galactose-tolerance test, might also be used

The method of enzyme assay may supplement or replace the galactose-tolerance test for several reasons Active indicator enzymes and coenzymes for testing have just recently become *commercially available* † *The enzyme assay is specific for* inherited galactosæmia [4] Moreover, galactose-tolerance testing may be contraindicated with neonatal jaundice, or with dehydration or hypoglycæmia Further, the task of investigating large numbers of cases by galactose-tolerance tests is formidable On the other hand, multiple enzyme assays may be done relatively rapidly by experienced technicians Four samples, including the internal standards, can readily be analysed in 2 hours The volume of blood required is small Blood from the umbilical cord can be used When necessary, arrangements should be made for collaboration with a laboratory doing the PGal uridyl transferase assay Red blood-cells can be obtained from centrifuged heparinised blood and stored *frozen until ready for shipment* [4]

If the transferase system is absent, complete investigation of the patient and his family is essential This should include slitlamp examination for cataracts, galactose-tolerance test, and PGal uridyl transferase assay of blood samples from other members of the family

It is not suggested that established brain damage can be improved This is a problem of the future Studies are at present under way of the effects of blocked galactose metabolism on the cells of microorganisms [7] Studies on cell and tissue cultures may shed further light on these problems

Childrens Hospital
Society of Los Angeles

WILLIAM R BERGREN
GEORGE DONNELL

National Institute of Arthritis and Metabolic Diseases U S Department of Health, Education, and Welfare, Bethesda, Maryland

HERMAN M KALCKAR

THE FALLACY OF THE FRACTURED CLAVICLE

SIR,—Mr Hicks (Jan 18) attempts to disprove what he considers to be a fallacy—namely, that the clavicle unites quickly and that this is promoted by incomplete immobilisation—by using another fallacy to do so It has long been recognised that clinical union of fractures often precedes radiographic union by a considerable period To use radiographic union as a standard is in itself a fallacy

Canterbury **F G ST CLAIR STRANGE**

ROYAL HOSPITAL FOR SICK CHILDREN, EDINBURGH

DR DOUGLAS GUTHRIE, 21, Clarendon Crescent, Edinburgh, 4, writes

"I have been requested to collect material for a short history of the Royal Hospital for Sick Children, Edinburgh, to mark the centenary of the hospital which will be celebrated in 1960 If any of your readers have letters, documents, or photographs relating particularly to the earlier years of the hospital which they would allow me to utilise, I should be most grateful"

Parliament

Multiple Packs

IN an adjournment debate on Jan 23 Dr J DICKSON MABON reminded the House that when the new National Health Service charge of 1*s* for each item on an E C 10 form was discussed, the Health Ministers had agreed to consider introducing multiple packs for some chronic patients, including diabetic, tuberculous, colostomy, and cardiac cases The new charge had been in force since Dec 1, 1956, and so far only one new pack, for the treatment of boils and carbuncles, had been introduced If the Government was finding it difficult to get professional agreement on the contents of possible new packs, and Dr Mabon himself did not think that they were a good idea, should not other ways of helping the chronic sick be considered? Would it, for instance, be possible to allow a doctor to prepare his own multiple packs from an approved list of variants? Or could a doctor issue numbered registration cards to his chronic patients, so that prescriptions bearing these numbers could be freed of charges?

Mr J NIXON BROWNE, *the joint under-secretary of State for* Scotland, said that when the new charges were introduced ten multiple packs were already on the market Examples of these were the syringe and spare needles for diabetics, the vaporiser set for bronchitic patients, and the multiple pack dressings for minor wounds Since then the Health Departments had been trying to devise further packs for chronic patients, and in this they had had the help of the British Medical Association But the only new pack that they had been able to devise that seemed likely to benefit enough patients to make its production useful was a *larger pack of dressings for general* use This proposal was at present before the manufacturers, who were considering the production arrangements It was hoped that it would be in chemists' shops in 8–12 weeks' time

Everyone was disappointed that it had not proved possible to devise new packs The main difficulty was the varied needs of *different* patients Before a pack could usefully be manufactured and marketed, it must be established that the standard contents would be suitable for a reasonably large number of patients, otherwise it would be impossible for the manufacturers to support its production *Mr Nixon Browne also* thought that the patient would prefer to have the items he needed precisely prescribed for him separately, rather than be given a standard pack *which did not* really meet his particular needs

Health of Office-workers

ON Jan 24 Mr VICTOR YATES *introduced as a private* member's measure the Offices Regulation Bill, which followed many of the recommendations of the Gowers report Besides empowering the *Home Secretary* to lay down minimum standards in every office for "structure, arrangement and operation" for the protection of the health, safety, and welfare of employees, the Bill also made special provisions for the fencing of dangerous machinery, the prevention of injury from electrical equipment, protection against the lifting of excessive weights, and the prohibition of the employment of women before and after childbirth

Mr DAVID RENTON, joint under-secretary of State for the Home Department, said that the Government supported the objects of the Bill But a measure to organise *conditions* in all offices was bound to be a major administrative and legislative exercise which could only follow consultation between Government departments, local and other public authorities, and

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* Obtainable from the Ames Chemical Company, Elkhart, Indiana, and Eli Lilly Company, Indianapolis, Indiana

† Obtainable from Sigma Chemical Company, St. Louis, Missouri

7 Kurahashi, K., Wahba, A. Unpublished studies

representatives of trades unions and employers' organisations Decisions would have to be taken at the highest level on methods of enforcement, administration, and cost It was therefore doubtful whether a private member's Bill would ever be suitable for this purpose. He agreed that private members' Bills had sometimes been successfully taken over by the Government, but such a procedure would not be suitable for this Bill because the necessary preliminary consultations had not taken place and because it left too many important questions unresolved But he wished to leave the House in no doubt that the Government accepted the need for the Bill and the principles which it covered A heavy programme had been announced for this session and it would be unwise to rush into legislation of this kind without adequate preparation and consultations

QUESTION TIME

Whitley Claim

Mr R J **Mellish** asked the Prime Minister if he would make a statement on his meeting with staff side Whitley Council (Hospital Staffs) held on Dec 23

Mr R A **Butler** I have been asked to reply Having heard the considerations put forward by the deputation from the staff side of the General Council of the Whitley Councils for the Health Services (Great Britain), on which the National and Local Government Officers Association was represented, the Prime Minister explained that the decision announced by the Health Ministers in relation to the pay of the administrative and clerical staff had been taken in the light of the need to maintain the position and purchasing power of the pound, and that the 3% increase could not be granted at the present time He agreed that the Whitley machinery in the health services needed to be reviewed, and said that in this context the points made by the deputation would be borne closely in mind

Mr **Aneurin Bevan** When the National Health Service was established and the Whitley machinery itself formed part of it, it was obvious that final responsibility must rest with the House of Commons because these were very large sums of money Is it not a fact that it was then hoped that the Whitley machinery would stand as a shield between the House of Commons and the workers involved? Would it not be wholly undesirable that large bodies of workers should be brought into conflict with the House of Commons and that wage-rates should be discussed on the floor of the House? If the Government persist in their attitude, would it not be necessary for us to have debates on wage-rates and to compare conditions with other conditions enjoyed by other members of the community, in which case, could it not easily happen that large bodies of workers in the country would come into conflict with the House of Commons and strike against the House of Commons?

Mr **Butler** One has to strike a balance between the sovereign power of the House of Commons and Parliament, the desire of hon Members to discuss matters of vital importance here, and the importance of preserving what the right hon Gentleman described as the shield of the Whitley machinery As I understand it, since the beginning of the National Health Service it has always been accepted that Whitley agreements must be in the form of recommendations to Ministers As Ministers are responsible to Parliament it is impossible to keep Parliament away from these problems I would add that the Minister of Health has deliberately said that he has undertaken to look at the Whitley aspect of this problem

Mr W W **Hamilton** asked the Secretary of State for Scotland if he had any further statement to make on the proposed pay increase for clerical staff within the National Health Service Mr J N **Browne** replied The staff side of the Administrative and Clerical Staffs Whitley Council lodged a claim on Jan 3 for a 5% increase to staffs on salaries up to £1200 per annum The council has agreed to defer consideration of the claim until Feb 12

Obituary

JOHN HUMPHREY THORNTON CHALLIS

M.R.C.S., F.F.A.R.C.S., D.A

Dr John Challis, senior anæsthetist to the London Hospital, died on Jan 21

Born in 1896, he was the son of the late Dr H T Challis He was educated at the City of London School and entered the London Hospital in 1913 As a lieutenant in the Royal Field Artillery (T.A) he left the hospital at the outbreak of the first world war and served in France and in many parts of the Middle East. Later he went with the British Forces to Russia, and afterwards to Ireland where he remained until 1922 Then, after 8 years of very varied and active service as a combatant, he re-entered The London and qualified in 1925 He spent the next 2 years in general house-appointments, alternating with periods in his father's general practice, before he began his career in anæsthetics In 1927 he became resident anæsthetist at The London and in 1931 was elected assistant anæsthetist to the hospital

His ability and capacity for work quickly won him a high reputation in his specialty, and his services were greatly in demand. In the '30s he visited America to study the new procedures, especially tracheal intubation, which he was introducing into this country He was elected also to the staff of many other hospitals, including the Southend-on-Sea General, King George V Hospital at Ilford, the Royal National Throat, Nose and Ear Hospital, Plaistow Maternity, Thorpe Coombe Maternity, and the Jubilee Hospital at Woodford Green.

In 1939, despite his many appointments, his age, and his long previous service, he transferred the commission he still retained in the Royal Artillery to the R A.M C , and following the outbreak of war went to France again. With the rank of major he was in command of a mobile neurosurgical unit. With this he retreated towards Dunkirk and with its many hundreds of wounded he was taken prisoner

The privations of the succeeding years undermined his health and though repatriated in 1943 he never fully recovered Debarred from most of the active pursuits, such as riding, which he had previously enjoyed, he never allowed disability to interfere with his work. He continued to contribute to medical literature and in 1947–48 was president of the anæsthetics section of the Royal Society of Medicine

Ten years ago he became senior anæsthetist to the London Hospital Of his work there J R E writes

Perhaps Challis's greatest achievement lies in his building up his department to meet the advances and increased demands of the last decade This he did with the efficiency and quietness that were so characteristic Always maintaining the highest standard of work, always cheerful, always kind and courteous, he was universally liked and respected His influence reached well beyond his own department, and his students rightly felt that from him they learned "doctoring" as well as anæsthetics He was an extremely modest man and spoke very little of his remarkably wide experience, but in his daily work and life he set an example of integrity and selflessness which could not be hidden Above all he set an example of courage Not even to those who knew him most closely did he ever complain about the cruel legacy of the last war, the disability of which inexorably increased His triumph over this affliction was not the least of his many achievements, but it was one he shared with his wonderfully happy and united family, his wife Dr Margaret Challis and their three daughters

His memory will last long in his hospital and will challenge and inspire many to aim at the high standard of service which he himself both set and bravely reached.

DOROTHY KIRBY PATERSON

M B Lond , D P H

Dr Dorothy Paterson, school medical officer and assistant medical officer for Southend-on-Sea, died at her home in Thorpe Bay on Jan 9 at the age of 43 From the Ilford County Girls' High School she won scholarships to the London School of Medicine for Women, and she qualified from the Royal Free Hospital in 1939 In 1948 she took the D P H and in the same year took up her appointment at Southend

J S L writes

Dr Paterson's duties were mainly connected with schools and schoolchildren, but she was also medical officer to the council's residential institutions for children and medical officer to the infant-welfare centre Her association with the nursery and children's homes was probably the most completely satisfying of all her professional activities , but her concern for the children went beyond their medical care, for she came to know some of them very well and interested her friends in the activities of the Homes To a wide clinical experience and excellent judgment there was added an instinctive and sympathetic understanding of children, who quickly gave her their trust As a colleague she was always helpful, self-effacing, and utterly reliable In recent months her friends noted with pleasure some lessening of her shy reserve and an enhancement of her natural serenity

Sir THOMAS DUNHILL

J W L writes

No account of the career of the late *Sir Thomas Dunhill* would be complete without mention of the fact that it was he who in 1932 founded the New End Hospital thyroid unit which, from small beginnings, has through the years increased out of all knowledge, not only in the number of patients treated, the size of its premises, its equipment, and the scope of its activities, but also in its reputation, which is nowadays not confined to the British Isles When in 1955 he watched the Duke of Edinburgh open a self-contained, readapted wing of the hospital, to be devoted entirely to the work of the thyroid clinic and department of endocrinology, he must, one thinks, have experienced a feeling of intense satisfaction in the knowledge that here, too, he had not laboured in vain

Appointments

BOYLE, CHARLES, M B Dubl , F R C S I senior casualty officer, Cardiff Royal Infirmary

BURNS, J P J , M C , M.B Belf , D P H deputy M O H , Islington

FERRY, G N , M B Brist assistant M O (school health, maternal and child welfare), Bristol

MAUGHAN, J H , M B Durh , D P H district M O H , Bridlington

MORAN, J G , L.R C.P I , D C H , D P H assistant M O (school health, maternal and child welfare), Bristol

RIORDAN, T P , M D N U I , D P M consultant psychiatrist/medical superintendent, Cefn Coed Hospital, near Swansea

SMITH, MARGARET I A , L.R C.P E , D OBST M O (maternity and child welfare), Manchester

East Anglian Regional Hospital Board

HAGUE, J M S , M B Lond surgical registrar, Ipswich and East Suffolk Hospital

HOOD, JAMES, M B Edin medical registrar, Newmarket General Hospital

ROSS, J G , B M Oxon surgical registrar, Ipswich and East Suffolk Hospital

SIMPSON, J C., M B Alberta surgical registrar, Ipswich and East Suffolk Hospital

Births, Marriages, and Deaths

DEATHS

CHALLIS —On Jan. 21, at his home, Green Rigg, Friary Lane, Woodford Green, Dr John Challis, beloved husband of Margaret.

BIRTHS

JACKSON.—On Jan 15, to Eileen Jackson M.B , and John W Jackson, M CH , F.R C.S of Cressingham Marsham Way, Gerrards Cross, Bucks —a son, Adam John Greenwood

Notes and News

A NEW AFRICAN MEDICAL SCHOOL ?

EIGHTEEN months ago a committee, with Mr Leslie Farrer-Brown as chairman, was formed to advise the University College of Rhodesia and Nyasaland on whether it should set up a medical school Last April the committee visited the three territories of the Federation, and now they have presented their first report, which the college is considering

They think that " the Federation will fall behind other communities comparable in area, population and growth unless it includes a medical school in its plans ", and they recommend that such a school should be established soon, because of the need for the local training of doctors and of the need and opportunity for research They regard it as axiomatic that the school should provide " a course of a university standard leading to a qualification which is registrable by the General Medical Council " Believing that a medical school should be integrated as closely as possible with the university of which it is part, they reject the claims of Bulawayo to be the most suitable place for the main teaching hospital, and propose instead that it should be formed round the nucleus of the new African hospital 7 miles from Salisbury Except when doing their medical or surgical clerking, the students should " live and study and play alongside the students of other faculties " The estimated cost of creating a medical school of the type recommended, with an intake of 25 students a year, is £1 million, and the annual expenditure would be £250,000

Besides the chairman, the committee consists of Prof W Melville Arnott, Prof T H Davey, Prof P B Medawar, Prof R Milnes Walker, Prof A D M Greenfield, and Dr Honor Smith

MAKERERE COLLEGE

FOR the University College of East Africa an important event of the last academic year[1] was that the General Medical Council recognised its licentiateship in medicine and surgery—the only African qualification so far recognised by the Council except those granted in the Union of South Africa

In the medical faculty much of the teaching is done by members of the Government Medical Service who are on the staff of the Mulago Hospital and act as part-time lecturers and collaborators in research, and sit on the faculty board Besides their teaching and heavy clinical work, the staff have found time for a great deal of research Some idea of the hard conditions in which this sometimes has to be done is given in the report of the department of obstetrics and gynæcology

> " The maternity department has been greatly overcrowded this past year, making teaching difficult, as mothers and babies often have to be discharged 24 hours after delivery through lack of beds Patients are often nursed and sometimes delivered on the floor "

An echoing theme in accounts of African medicine is the want of doctors The department of surgery organised no postgraduate course because the lack of doctors prevented the Government from releasing enough from duty to warrant a formal course In the department of obstetrics, " leave periods mean very heavy work for the staff left behind it makes it very difficult to find time for adequate research " The department of pathology was forced to reduce the number of formal laboratory classes because " Government pathologists have simply not got the time to assist in teaching large laboratory classes " It is indeed heartening that, for all these handicaps, Makerere College is successfully training the African doctors who will eventually fill these great gaps

WORLD HEALTH ORGANISATION

THE Executive Board, meeting in Geneva, has decided to ask the Director-General to study the possibility of including sports medicine in the programme of W H O Proposing this, the four Scandinavian countries pointed out that our way of life, as machines are used more and more, leads to a lessening of physical activity, and coronary-artery disease, for instance, is commoner in those whose occupations involve less physical work. Sports are increasingly practised, " as they satisfy man's apparently instinctive urge for motion", in turn they invite consideration of their effects on health and longevity, the prevention of accidents, and their mental-health aspects The proposal urges W H.O to take the lead in sports medicine

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[1] Makerere College the University College of East Africa Report for the year 1956–57 Obtainable from P O Box 262, Kampala Uganda

In the yaws eradication campaign, half the 200 million people exposed to the disease will have been examined, and 25 million treated with penicillin, by the end of this year Most of the remaining 100 million live in Africa, where populations are scattered and there is not much money, the campaign is expected to take about ten years What can be done is shown by the fall in the prevalence of yaws, since the campaign began, in Western Samoa (from 11% to 0 04%) and Haiti (from 36 5% to 0 57%)

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names

Approved name	*Other names*
*Alphacetylmethadol	α-3-Acetoxy-6-dimethylamino-4 4-diphenylheptane *O*-Acetate of α-6-dimethylamino-4 4-diphenylheptan-3-ol
*Alphamethadol	α-6-Dimethylamino-4 4-diphenylheptan-3-ol
Azacyclonol	Diphenyl-(4-piperidyl)methanol Frenquel is the hydrochloride
*Betacetylmethadol	β-3-Acetoxy-6-dimethylamino-4 4-diphenylheptane *O*-Acetate of β-6-dimethylamino-4 4-diphenylheptan-3-ol
*Betamethadol	β-6-Dimethylamino-4 4-diphenylheptan-3-ol
†Bromodiphenhydramine	2-(4-Bromodiphenylmethoxy) ethyldimethylamine 4-Bromo-α-phenylbenzyl 2-dimethylaminoethyl ether Ambodryl
Chlorothiazide	6-Chloro-7-sulphamoylbenzo-1 2 4-thiadiazine 1 1-dioxide Chlotride, Diuril, Saluric
Choline Theophyllinate	Choline salt of theophylline Choledyl
Cyclopregnol	6β-Hydroxy-3 5-*cyclo*pregnan-20-one Neurosterone
Cycloserine	*D*-4-Aminoisoxazolid-3-one Seromycin
Deserpidine	11-Demethoxyreserpine Harmonyl
*Desomorphine	Dihydrodeoxymorphine
*‡Dimepheptanol	6-Dimethylamino-4 4-diphenylheptan-3-ol Methadol
Diphenylpyraline	Diphenylmethyl 1-methyl-4-piperidyl ether Histryl is the hydrochloride
*Etoxeridine	Ethyl 1-[2-(2-hydroxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate
Hexocyclium Methylsulphate	1-(2-*cyclo*Hexyl-2-hydroxyphenethyl)-4 4-dimethylpiperazinium methylsulphate Tral
Hydromorphone	Dihydromorphinone Dilaudid is the hydrochloride
Mannomustine	1 6-Di-(2-chloroethylamino)-1 6-dideoxy-*D*-mannitol Degranol is the dihydrochloride
*Methyldesorphine	6-Methyl-Δ^6-deoxymorphine
*Metopon	Dihydromethylmorphinone
*Myrophine	Myristyl ester of benzylmorphine
Nandrolone	17β-Hydroxy-19-norandrost-4-en-3-one 19-Norandrostenolone 17β-Hydroxyoestr-4-en-3-one Durabolin is the phenylpropionate
Oxycodone	Dihydrohydroxycodeinone Eucodal is the hydrochloride
*Oxymorphone	Dihydrohydroxymorphinone
Promazine	10-(3-Dimethylaminopropyl)phenothiazine Sparine is the hydrochloride
Proquamezine	10-(2 3-Bisdimethylaminopropyl)phenothiazine
Thalidomide	α-Phthalimidoglutarimide Distaval
Thebacon	Acetyldihydrocodeinone
*Trimeperidine	1 2 5-Trimethyl-4-phenyl-4-propionyloxypiperidine

University of Aberdeen

Dr E Maurice Backett, senior lecturer in social medicine at Guy's Hospital and at the London School of Hygiene and Tropical Medicine, has been appointed to the new chair of social medicine at Aberdeen. He is expected to take up his appointment in October

Dr Backett, who is a bachelor of medicine and science of the University of London, qualified from Westminster Hospital in 1944 After working on the research staff of the Air Ministry, he held a Nuffield fellowship in social medicine and later joined the Medical Research Council's social medicine research unit. Before taking up his present post he was lecturer in social medicine in the Queen's University, Belfast. He took the M.R.C.P. in 1950 and the D.P.H. in 1955 His published work includes studies of general practice, of the social care of deaf mutes, and of the social pattern associated with the spread of infection by poliovirus More recently, with other members of the unit, he has been inquiring into the incidence of road accidents among children and of coronary disease in doctors

University of Edinburgh

Dr W L M Perry, director of the Department of Biological Standards at the National Institute for Medical Research, London, has been appointed to the chair of materia medica in succession to Prof J H Gaddum who is retiring

Dr Perry qualified from the University of St. Andrews in 1943 and took the degree of M.D five years later After holding house-appointments at the Royal Infirmary, Dundee, he became a medical officer in the Colonial Medical Service, and was stationed in Nigeria. He joined the scientific staff of the Medical Research Council in 1947 His research has been mainly concerned with the autonomic nervous system. In 1952 he was appointed to his present post, in which he has of late years been closely concerned with controlling and testing the British poliomyelitis vaccines He was appointed O.B.E. in 1957

The university court has announced that Sir Stanley Davidson will retire from the chair of medicine at the end of March, 1959

Dr A. A Shivas has been appointed lecturer in the department of pathology, and Dr J F Lamb lecturer, and Dr M Jacobsen assistant, in the department of veterinary physiology

National Institute for Medical Research, London

Dr D G Evans has been appointed director of the Department of Biological Standards at the institute in succession to Dr W L M. Perry, whose appointment to a university chair is announced above. At present Dr Evans is head of the control laboratory of the department.

University of Adelaide

Mr R. P Jepson, professor of surgery in the University of Sheffield, has been appointed to the chair of surgery

Royal College of Physicians of London

On Thursday, Feb 13, at 5 P.M at the college, Pall Mall East, S W 1, Dr A. L Cochrane will give the Marc Daniels lecture. His subject will be the meaning of the X-ray classification of coalworkers' pneumoconiosis

Reticuloendothelial Society

The second symposium of this society will be held in Rapallo, Italy, from Aug 29 to 31

It is intended to discuss the subject under three main headings the reticuloendothelial system and steroids, the reticuloendothelial system and immunity, including antibody immunity and properdin, and tumour immunity, and the reticuloendothelial system and radiation. Proposed titles of papers should be sent, with a brief summary in English, before March 15, to Dr Alberto Marmont (Clinica Medica Universitaria, Viale Benedetto XV, Genoa, Italy), who will notify accepted speakers

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* Narcotic substances which fall under International Conventions and are not available as therapeutic agents

† Replaces the approved name bromazine from May 1, 1958

‡ Replaces the approved name methadol.

Royal College of Obstetricians and Gynæcologists

At the meeting of council held on Jan 25, with Prof Andrew Claye, the president, in the chair, the following were elected to the membership

Vijayaratnam Balachandran, Bholanath Banerji, S K Basu, F X Bencini, Olga Bolitho, R T Booth, Carolina A Braga, A F Bushby, A S F Butcher, D P Das, F J De Maria, R E F Devitt, P H Drake, I MacD Duthie Mary G Eldridge, Denys V I Fairweather, F G Feinstein, N K Ghose, P R G Gordon, H M Gough, J L Hanington, G H Harris, J C Hartgill, C. H Hodge, Helena E Hughes, T R Hunt, A H John, Satyadev Khanna, Herbert Kramer, Dorothy K C Kwan, D J Mackay, Patricia C Mackay, Sheila A Martyn, Gillian G Matthews, R J Mitchell, A K Mukherjee, Jean M North, Joan North, O K Ogan, W H Patterson, P A Rachow, Krishna Sankari, Bernard Shieff, Ma Khin Si, Margaret L Smith, I H F Swain, Mary A T Tolley, R D Upton, Beoin Cleote Uys, A J Van Amerongen, J A Verzin, D W Warrell, James Willocks

The Human Brain

On Feb 6, 12, and 18 at 5 15 P M lectures on this subject will be given at Bedford College, Regent's Park, London, N W 1 The speakers will be Prof J Z Young, Dr D M. MacKay, and Dr W Grey Walter

Faculty of Homœopathy

At a meeting of this faculty to be held at the Royal London Homœopathic Hospital, Great Ormond Street, W C 1, on Thursday, Feb 6, at 5 P M, Dr Alva Benjamin will speak on the medical profession's responsibility for the health of the community

North of England Obstetrical and Gynæcological Society

The following officers have been elected for this society for 1958

President, Dr E A Gerrard, vice-presidents, Miss M Evans, Mr C J K Hamilton, Mr G W Theobald, Prof C S Russell, and Mr F J Burke, hon treasurer, Mr C H Walsh, hon general secretary, Miss E Mills, hon reporting secretary, Miss U M Lister

Child and Family Psychiatry

The department of child and family psychiatry of the Ipswich and East Suffolk Hospital is holding a course on this subject from March 24 to 28

The course is open to doctors and places will be allocated in order of application to 11, Fore Street, Ipswich

Work in Compressed Air

The Work in Compressed Air Regulations, published last August in draft form (see *Lancet*, 1957, ii, 333), are to come into operation on April 21

Liverpool University Medical Students' Society

The annual dinner for past and present members of this society will be held at the Mecca Sefton House, Liverpool, on Feb 6 Dr E T Baker-Bates will be in the chair and the guest of honour will be Dr T Leslie Dowell Tickets (25*s*) may be had from the medical dinner secretary, Medical School, University, Liverpool, 3

Medical Art Society

This society will hold its annual exhibition at Walker's Galleries, 118, New Bond Street, London, W 1, from Thursday, Feb 13, to Wednesday, March 5

International Collegium for Neuro-Psychopharmacology

The first of these international symposia will be held in Rome from Sept 9 to 12 Those interested in presenting papers are asked to send a 250-word abstract before March 31 to Dr P B Bradley, department of experimental psychiatry, Medical School, Birmingham, 15

The Hurt Mind

Four of the B B C television programmes on mental health which were transmitted under this general title last year, are now available in 16 mm film form (*Put Away*, 5 reels, £1 5*s* 46 minutes, *Break-down*, 3 reels, 15*s* 29 minutes, *Psychological Treatment*, 3 reels, 15*s* 30 minutes, and *Physical Treatment*, 3 reels, 15*s* 33 minutes) They can be hired from the Central Film Library, Government Building, Bromyard Avenue, Acton, London, W 3

Dr J C. M Matheson, principal medical officer at Brixton Prison is retiring after 28 years in the Prison Service

Diary of the Week

FEB 2 TO 8

Monday, 3rd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr Brian Ackner Emotions and the Cardiovascular System

Tuesday, 4th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S W 1
5 P.M Dr Cicely Williams Social Medicine in Developing Countries (First of two Milroy lectures)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr M G P Stoker Growth of Viruses

ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Mr J D S Flew Induction of Labour

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr C. D Calnan Hæmangiomata

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr G C Knight Spinal Cord Lesions

Wednesday, 5th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 15 P M *History of Medicine* Sir Weldon Dalrymple-Champneys Preventive and Curative Medicine in Ancient Peru (Presidential address)
5 30 P M *Experimental Medicine and Therapeutics* Prof C. Rimington, Dr A C Allison, Dr H V Ingram, Dr J Walters Hæmoglobin
8 P M *Surgery* Mr R V Cooke, Prof John Bruce Small Bowel Obstruction

POSTGRADUATE MEDICAL SCHOOL
2 P M Dr A E Mourant Blood-groups and Human Races

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr Paul Wood Current Problems Relating to Congenital Heart disease

INSTITUTE OF DERMATOLOGY
5 30 P M Dr R W Riddell Ætiology of Fungous Infections

ASSURANCE MEDICAL SOCIETY
5 P M (11, Chandos Street, W 1) Dr J L Livingstone Asthma and Bronchitis in Relation to Life Assurance

MIDLAND MEDICAL SOCIETY
8 15 P M (36, Harborne Road, Edgbaston, Birmingham, 15) Dr Dorothy Campbell Medical Treatment of Glaucoma

NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY, 64, St James's Street, Nottingham
8 30 P M Mr T N MacGregor Causation and Prevention of Perinatal Mortality

MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *Medicine* Prof Walter Schlapp Charles Scott Sherrington—An Anniversary (Presidential address)

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (18, Nicholson Street, Edinburgh) Dr J Halliday Croom Management of Diabetes

Thursday, 6th

ROYAL COLLEGE OF PHYSICIANS
5 P M Dr C Williams Social Medicine in Developing Countries (Second of two Milroy lectures)

UNIVERSITY OF LONDON
5 P M (Middlesex Hospital Medical School, W 1) Prof T S Westoll Pattern and Form in the Vertebrate Skull

ROYAL SOCIETY OF MEDICINE
8 P M *Neurology* Mr D W C Northfield Dr Denis Hill, Mr Murray Falconer Surgery of Temporal Lobe Epilepsy

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr C. S Hallpike Remarks upon the Scientific Basis of Otological Practice

NUFFIELD ORTHOPÆDIC CENTRE, WINGFIELD MORRIS ORTHOPÆDIC HOSPITAL, Oxford
8 30 P M Prof Myer Makin Surgical Management of Friedreich's Ataxia

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P M Dr Thomas Black Marcello Malpighi and his Influence on our Knowledge of the Spleen

Friday, 7th

ROYAL SOCIETY OF MEDICINE
10 30 A M *Otology* Prof L Ruedi, Mr A Tumarkin, Dr J F Birrell Cholesteatosis of the Attic
2 30 P M *Laryngology* Dr C H Andrewes, Prof C H Stuart Harris Virus Infections of the Upper Respiratory Tract
5 30 P M *Anæsthetics* Dr P L. Mollison Recent Advances in Transfusion

POSTGRADUATE MEDICAL SCHOOL
10 A M Sir Cecil Wakeley Surgery of the Breast
4 P M *Dr I McD G Stewart Changing* Ideas about Hypertension

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Dr Norman Hulbert Functional Factors in Ear, Nose, and Throat Diseases

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CORRIGENDUM *Research on Schistosomians in China*—In the second paragraph of a note describing the work of Prof C P Mao (*Lancet*, 1957, ii, 498) lines 5, 6, and 7 up to "fertiliser" should have been omitted, and the following words should have appeared at the end of the paragraph "Schistosome eggs contained in the night-soil are destroyed either by composting or by storage, especially when calcium cyanamide (which is a useful fertiliser) or urine (which produces ammonia) is mixed with the fæces"

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RESULTS OF NYLON-DARN REPAIRS OF HERNIÆ

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EVERY medical-school boy knows what to do to cure rupture, even though he may become a medical statistician or a member of parliament. We had hints on sacs and their coverings in our pregestational preclinical period, we were weaned into clinical surgery by the study of lumps in the groins, a part of every surgical childhood is assisting at a hernia operation, and much of the puberty of an operating surgeon is passed in attempts to contain the results of Nature's foibles and caprices in the inguinal region. Yet, in spite of this universal familiarity, few realise that operations for rupture, though among the most ancient of operations, still usually produce results far from the ideal of a complete and permanent cure. Though most of this tale is stale, the subject merits repeated review, because operations for hernia are among those most commonly performed.

Surveys and pronouncements of results are chiefly of value where long-term results are assessed. MacLeod (1955) has shown the fallacy of relying, in adults, on simple herniotomy and repair of the fascia transversalis at the internal ring. He claims that his own results with these simple methods were so poor that he has published them as a warning to others—a most magnanimous gesture. The results of different repairs done by various surgeons are shown in table I and speak for themselves. One notable point is the scarcity of reviews made more than 2 years after operation. Douglas (1953), with a report on tantalum mesh at 5 years, and Shouldice (1953), with a review of recurrent herniæ at 4 years, are the only ones to give clearly defined long-term figures.

Another point appearing from table I is that the use of the patient's own tissues for repair did not appear to give so high a percentage of permanent results as when either silk or metal was incorporated in the repair. The concrete of fibrosis does not seem to be so good at withstanding strains as does the reinforced concrete of a permanent mesh embedded in fibrous tissue.

Gupta (1954) boldly proclaims that the figures for recurrent inguinal hernia are 15–30%, and table I confirms that some salvos fall within that range, though others appear to be distinctly nearer the target of no recurrence.

Hagan and Rhoads (1953), to find out how long after the initial operation recurrences may be expected, analysed the histories of 75 patients presenting with recurrent herniæ. They found that 55% of recurrences had occurred in 2 years, 75% in 5 years, and 85% in 10 years, and they depressingly noted that recurrences may appear as late as 40 years after operation. One is tempted to believe that a further survey might break this record by revealing a recurrence after half a century. Since at 40 or 50 years both the surgeon and the patient may defy record-breaking attempts by dying, I am among those neither ambitious nor patient enough for that attempt and am prepared to settle for the simple solution of finding the true recurrence-rate by multiplying a 5-year result by 4·3.

Moloney et al (1948) advocated the use of a darn of monofilamentous nylon for the repair of herniæ, agreement being expressed with the views of other workers who said that five years should elapse before it is worth while reviewing the recurrence-rate. Accordingly I now review 253 nylon-darn repairs for inguinal herniæ (222 in males in whom 22 were recurrent, and 31 in females) all done by me more than 5 years previously.

Moloney et al (1948) claimed that monofilamentous nylon stood up to the misfortune of sepsis better than did anything previously used, and was therefore particularly valuable for strangulated herniæ because of the potential infection of these wounds. This view has been substantiated by this present study, which includes a survey of the effect of nylon sutures on the healing of 2181 repairs of different varieties of hernia done by the general surgeons and their assistants at the Radcliffe Infirmary and the Churchill Hospital in the 9 years of 1946–54.

TABLE I—RESULTS OF REPAIR OF INGUINAL AND FEMORAL HERNIÆ BY VARIOUS SURGEONS

Reference	No	Type of hernia	Type of repair	% traced	Length of follow-up after last operation	Recurrence-rate (%)	Remarks
MacLeod (1955)	255	Primary inguinal	Various	90	2 yr	12·8	Males aged more than 17
	34	Recurrent inguinal	Various	90	2 yr	36·7	
	161	Primary inguinal	Simple herniotomy	83	2 yr	14·3	
	92	Inguinal	Posterior silk-lattice repair	92	2 yr	8·2	
Mair (1946)	113	Inguinal	Whole skin	76	1 yr	1	
citing 4 authors	320	Indirect inguinal	McArthur fascial	?	1–3 yr	3·0–9·3	
citing 2 authors	188	Indirect inguinal	Gallie repair	?	1–1½ yr	7·0–9·2	
citing 9 authors	More than 1000	Direct inguinal	Bassini	?	?	5–30	Including Page (1943) operations on London Police 25·8%
Rose (1953)	50	Inguinal	Full thickness skin-graft	?	2 yr	6	
Palumbo and Mighell (1954)	867	Primary indirect inguinal	Cotton or silk Halsted-Bassini	87·7	1 yr	1	
Hagan and Rhoads (1953	74	Primary femoral	? Imbrication in layers of various suture materials	71	2 yr	2·9	
	219	Primary direct inguinal		?	2 yr	5·1	Mortality 0·29%
	714	Primary indirect inguinal		?	2 yr	4·1	
	75	Recurrent inguinal		?	2 yr	21	
Koontz (1951)	[illegible]	Inguinal	Tantalum mesh		1–30 mos	1·3	Herniæ with large defects and poor tissues
Douglas (1953)	32	Various large recurrent	Tantalum mesh	100	5 yr	6·3	Recurrences both inguinal
Abel and Hunt (1948)	300	Various	Steel-wire darn	No follow-up	0–? yr	See text	General report on 10 years experience of wire in abdominal wall
Shouldice (1953)	8317	Inguinal and femoral mostly	Silk or steel wire	60	10 mos – 10 yr	1·03	
	111	Recurrent inguinal or femoral	Steel wire (? some silk)	58·5	4 yr	3·1	
Ryan (1953)	150	Recurrent inguinal and femoral	Steel wire (? some silk)	100	2 yr	1·3	

TABLE II—ANALYSIS OF WOUND DISTURBANCES AFTER HERNIÆ
(2181 repairs in 1973 patients [235 with strangulation, 1738 without strangulation])

Type of hernia	No	Stitch and superficial sepsis	Hæmatoma without discharge	Deep sepsis (immediate and delayed) or discharging hæmatoma	Resulting sinuses needing removal of nylon	Nature of sutures		Resulting sinuses not needing removal of nylon	Nature of sutures	
						Braided	Monofilamentous		Braided	Monofilamentous
Inguinal										
Strnagulated	118	0	0	5	3	3	0	2	0	2
Non-strangulated	1671	15	15	19	11	7	4	8	3	5
Femoral										
Strangulated	88	1	0	3	0	0	0	3	0	3
Non-strangulated	108	0	2	2	2	2	0	0	0	0
Incisional										
Strangulated	13	0	See text	0	0	0	0	0	0	0
Non-strangulated	80	0	"	7	3	3	0	4	1	3
Umbilical										
Strangulated	16	0	See text	2	1	1	0	1	0	1
Non-strangulated	87	0	"	2	0	0	0	2	1	1
Total	2181	16 (*0 7%*)	17 (*0 7%*)	40 (*1 9%*)	20 (*0 9%*)	16 (*0 6%*)	4 (*0 4%*)	20 (*1%*)	*5*	15

Of 21 sinuses containing braided nylon 16 needed removal of sutures (in 1000 repairs)
Of 19 sinuses containing monofilamentous nylon 4 needed removal of sutures (in 1000 repairs)

Both varieties of nylon, braided and monofilamentous, were used in these two hospitals, and various surgeons, myself included, used both varieties at different times The number of times that each variety was used was estimated by a survey of the operation notes (which do not always state this detail) and in other ways For the general assessment of results it can be assumed that, of about *2000* nylon darns, about *1000* were repaired with braided nylon and 1000 with monofilamentous nylon

Analysis of Wound Disturbances in 2181 Repairs

Strangulated and non-strangulated herniæ are separately analysed (table II), but the results for both and for the various varieties of abdominal herniæ are totalled

Stitch and Superficial Sepsis, and Hæmatoma, without Discharge

Stitch and superficial sepsis occurred in 0 7% and hæmatoma without a discharge from the wound also in 0 7%

Because of the large size of many incisional and umbilical herniæ there often remains in the superficial fat, after the aponeurosis has been repaired, a large cavity which is at times difficult to obliterate completely Therefore the incidence of hæmatoma after these repairs is higher than that following repairs in the inguinal and femoral regions, where the closure is easier The exact incidence after the repair of large ventral herniæ was very difficult to ascertain from the postoperative notes, which did not state clearly whether or not a hæmatoma had formed and what was primarily a hæmatoma and what sepsis In consequence there was no attempt with ventral herniæ to separate the categories of hæmatoma, immediate sepsis, and delayed sepsis, but hæmatomata following inguinal and femoral repairs were analysed and are shown in table III The only conclusion, from such small figures, is that, in a wound showing a large hæmatoma, healing can sometimes take place without the need for removal of nylon sutures, but sometimes removal may be necessary to promote healing

Deep Sepsis (Immediate and Delayed) and Discharging Hæmatoma

This occurred in *1 9%* of *2181* repairs (table IV)

Immediate deep sepsis was considered as sepsis developing within two weeks of operation, and, for reasons already given, deep sepsis was assessed for inguinal and femoral herniæ only In *1985* inguinal and femoral repairs (strangulated and non-strangulated) immediate deep sepsis developed in 13 cases (0 7%) Out of all the many instances of potential infection, especially with strangulated herniæ, and the 13 instances of freely discharging wounds it was necessary to remove nylon from

TABLE III—ANALYSIS OF WOUNDS SHOWING HÆMATOMA
(Inguinal and femoral herniæ only)

Type of hernia	No	With unbroken wound	With temporary sinus healing	Type of suture		Sinus needing removal of nylon	Type of suture	
				B	M		B	M
Inguinal								
Strangulated	118	0	1	0	1	0	1	2
Non-strangulated	1671	15	3	1	2	3		
Femoral								
Strangulated	88	0	0			0		
Non-strangulated	108	3	0			0		
Total	1985	18	4	1	3	3	1	2

B, braided M, monofilamentous

TABLE IV—ANALYSIS OF WOUNDS SHOWING DEEP SEPSIS
(Inguinal and femoral herniæ only)

Type of hernia	No	Immediate sepsis							Delayed sepsis				
		No	Removal of nylon	Type of nylon		No removal of nylon	Type of nylon		No	Removal of nylon	Type of nylon		No removal of nylon
				B	M		B	M			B	M	
Inguinal													
Strangulated	118	1	0	1	1	1	0	1	3	3	3	0	0
Non-strangulated	1671	9	2			7	3	4	6	6	5	1	0
Femoral													
Strangulated	88	3	0			3	0	3	0	2	2	0	0
Non-strangulated	108	0							2				
Total	1985	13 (*0 7%*)	2 (*0 1%*)	1	1	11 (*0 6%*)	3	8	11 (*0 6%*)	11 (*0 6%*)	10	1	0

B braided *M*, monofilamentous

the wound to heal sinus formation in only 2 instances (1 monofilamentous and 1 braided). This is clear enough evidence that herniæ repaired with nylon stand up well to the misfortunes of both potential infection and immediate frank sepsis, and generally heal without the need for removal of the nylon.

Delayed deep sepsis is a different matter. It was analysed in detail only for inguinal and femoral herniæ (strangulated and non-strangulated), and a striking result was found. Monofilamentous nylon is seen to be almost completely innocent as a trouble-maker, whereas braided nylon compares very badly, being found to be no better than silk and thread in its inability to stay in the tissues in a high proportion of instances. Delayed sepsis developed in 11 cases (0·6%), of which 10 were with braided nylon, and the only time that it developed with monofilamentous nylon a layer of thread had also been used in the repair.

TABLE V—COMPARISON OF HEALING OF INFECTED WOUNDS SUTURED WITH NYLON OR WITH CATGUT AFTER APPENDICECTOMY

—		Severity			
		1	2	3	4*
Catgut	Number of cases	336	208	83	64
	Percentage with wound sepsis	8	28	37	50
	Percentage with late discharge of suture	2	5	8	9
Nylon	Number of cases	119	70	49	35
	Percentage with wound sepsis	3	6	10	10
	Percentage with late discharge of suture	1	3	2	5

(Modified from a table in *British Journal of Surgery*.)
* General peritonitis

This delayed reaction appears to be due either to sepsis or to a foreign-body reaction, and it has been noted before, especially by Edwards (1943) in his review of recurrent hernia in soldiers, when he called attention to the reaction with silk and in consequence made a plea for abandoning the use of floss silk as a material for repair. In this reaction the wound appears to heal well, and then, at a variable interval after operation, a swelling develops which eventually discharges on to the surface. The times of onset of this development in those instances after inguinal repairs were 1, 3, 3, 5, 18, and 18 months after non-strangulated cases and 2, 3, and 3 months after strangulated cases. This series under analysis was completed in 1954, and there was no trace of this delayed reaction developing later than 18 months after operation.

Nylon has been given a bad name for sinuses in some quarters, and this appears to be justified for braided nylon. This tendency for a high rate of sinus formation after the use of braided nylon has been noted in the closure of abdominal wounds, and for this reason, after trying it for a time, I completely abandoned its use in favour of monofilamentous nylon.

TABLE VI—BOWEL RESECTIONS AND DEATHS

Type of hernia	Bowel resections (strangulation only)	Deaths (all causes)
Inguinal		
Stranuglated	7	6
Non strangulated		1
Femoral		
Strangulated	15	6
Non strangulated		0
Incisional		
Strangulated	1	1
Non strangulated		1
Umbilical		
Strangulated	5	2
Non strangulated		0
Total	28 (*12%*)	17 (15 strangulated) S 6·3% Non S 0·01%

TABLE VII—PERSONAL SERIES OF INGUINAL REPAIRS
(219 patients repaired more than 5 years, 76% contacted)

Total sides	Superficial sepsis	Deep sepsis		Discharging hæmatoma	Recurrence	Died
		Immediate	Delayed			
253	1	1 monofilamentous (sutures removed)	1 braided (sutures removed)	1 monofilamentous (sutures removed) 2 scrotal (monofilamentous) incised and healed	2 (1 braided after enormous recurrent defect 1 monofilamentous after hæmatoma)	1 (acute retention, prostatectomy)

Monofilamentous nylon appears to be a reliable suture. In this series, when it was used in 1000 repairs of all variety of herniæ, sutures had to be removed on only four occasions to heal sinuses. Should the removal of monofilamentous nylon be necessary, this is a simple matter owing to the ease with which it slides through the tissues compared with the great difficulty of excising a braided suture, which does not readily move along its track when pulled on. There was one recurrence associated with the removal of the sutures, an instance of hæmatoma following one of my own operations and leading to sinus formation in a wound which would not settle until the sutures were removed.

Over 100 strangulated inguinal and femoral herniæ were repaired with an immediate darn of monofilamentous nylon with no instance of nylon removal. Table II shows that monofilamentous nylon stood up well to sepsis after strangulation. Braided nylon produced 3% of sinuses in the strangulated inguinal repairs.

TABLE VIII—RETURNED RECURRENCES
(In 2181 repairs in 1973 patients by general surgical staff)

Type of hernia	No	Recurrences	After wound sepsis	After hæmatoma	After primary healing
Inguinal					
Strangulated	118	3 (*3·0%*)	0	1	2
Non-strangulated	1671	6 (*0·4%*)	0	1	5
Femoral					
Strangulated	88	1 (*1·0%*)	1	0	0
Non-strangulated	108	0	0	0	0
Incisional					
Strangulated	13	0	0	0	0
Non strangulated	80	7 (*9·0%*)	4	0	3
Umbilical					
Strangulated	16	2 (*13·0%*)	2	0	0
Non-strangulated	87	1 (*1·0%*)	1	0	0
Total	2181	20 (*1·0%*)	8	2	10

There is no justification for the method of "repairing" strangulated cases with catgut initially and repairing the recurrences by sounder means, because wound troubles are more likely if catgut is used. This was shown in an analysis made by Moloney et al. (1950) of the comparative sepsis-rate in wounds contaminated with septic material in operations for acute appendicitis and sutured either with nylon or with catgut and shown in table V. The table apparently shows that infected wounds sutured with nylon heal better and discharge the sutures less frequently than do those sutured with catgut. Every substance used for suture can cause a sinus, steel and tantalum included, but other comparative figures are not available to match those for monofilamentous nylon, which in this series of herniæ was responsible for 0·4% of sinuses.

Comments on Patients with Strangulated Herniæ and on Deaths

The number (12%) of necessary resections of bowel in strangulated herniæ (table VI) shows that delay is as dangerous as ever, and the absence of bowel resections in the elective group confirms again that the best time to treat a hernia is before it strangulates The low incidence (6·3%) of deaths in the strangulated group is an index of satisfactory treatment but still re-emphasises the great danger of strangulation In the elective group there were 2 deaths, one pointing to the constant need for care in assessing the urinary system before attempting the repair of hernia in the elderly patient, and the other emphasising the danger inherent in the treatment of a large incisional hernia, this patient developing intestinal obstruction after the operation

Recurrence Rate

5-Year Follow-up of Personal Series of Inguinal Herniæ

For the purpose of studying the incidence of recurrence I made a study of my own patients operated on in 1946–51 (table VII), all patients being operated on more than 5 years previously All types of herniæ were studied, but only the numbers for inguinal herniæ were large enough to be profitable for conclusions

As is usual in such searches, it was found that several patients had emigrated overseas and others had died from causes unconnected with their hernia Still other patients could not be traced

At the end of the search about 76% of 219 patients who had submitted to about 253 inguinal repairs were found and replied to the questions All the patients had been seen at the hospital outpatient clinic 6 months after the operation, and from this source and from their replies there was nothing to suggest that any testicular atrophy or hydrocele had resulted from the operation The only recurrent herniæ which were traced by this survey and from a study of the patient's notes after further visits to the hospital for follow-up for herniæ or other causes were 2 patients who were returned because of further trouble

(1) A man, aged 51, had both a direct inguinal hernia and a femoral hernia on the one side, and the repair did not settle well after the operation, the wound having the appearance of a deep hæmatoma The hardness was replaced by a mass which did not settle, and after a year a recurrence was evident A bunched-up mass of monofilamentous nylon was excised at the site of the old hæmatoma, and a direct weakness was repaired with a further darn of monofilamentous nylon, and there has been no further trouble in the past 4 years

(2) A man, aged 83, had been operated on previously by one of my assistants for a massive inguinal hernia which had strangulated Because of the poor state of the patient the repair was not thorough, and the hernia had recurred within 3 months The defect was huge, the contents of the sac being half the contents of the abdominal cavity, and the tissues were poor, the problems being more those of a large incisional hernia than of the usual inguinal hernia Because of the recurring attacks of pain I decided to try to repair the defect, again braided nylon being used All the ligamentous tissue below had shorn away, and the only remaining soft tissue below was muscle and fascia, into which I darned the nylon Within 5 months the patient had returned again with a huge defect While we were wondering how to stem the bulge, the patient freed us of further anxiety on his account by rupturing his aorta

These two cases are the only traceable recurrences (0·8%) from the 253 inguinal repairs after 5 years

" Return " Recurrences in General

In the total series of 2181 repairs done in the 9 years from 1946–54 by the general surgeons and their staff in the United Oxford Hospitals—the recurrence-rate was studied by a search of follow-up notes and subsequent admissions because with such large numbers, an approach to each patient was impracticable This incomplete assessment of the recurrence-rate was therefore made only on " returned " recurrences, but the figures are included for what they are worth (table VIII) They do at least suggest that the low rate of " returns " after nylon-darn repairs in strangulated cases is a strong pointer to its potential usefulness in strangulation Since patients are usually fairly sympathetic towards a surgeon who has initially saved their lives, if those patients develop recurrences they are less likely to go outside their own district for subsequent treatment, and, since the two hospitals concerned in this survey are the only ones serving the area, " return " and true recurrence-rates are therefore likely to coincide closely in this instance

Inguinal Repairs

Of 1789 inguinal repairs 6 recurrences returned to us, including the 2 of my own Of the 4 others, 2 were after repairs by one of my house-surgeons, and, when I reoperated on both herniæ, it was quite clear from the sites of the recurrence that the darns had been incompletely done at the medial ends of the inguinal canal—a common cause of recurrence The same remarks apply to the other 2 instances of recurrence, which were not under my care

Strangulated Inguinal Herniæ

There were 3 recurrences in 118 repairs, 1 being the recurrence already mentioned of the large hernia in the patient who finally ruptured his aorta The 2nd recurrence followed a repair by a house-surgeon who had clearly not darned the canal adequately The 3rd was that which followed a bloc-excision of a mass of tissue in the inguinal canal for removal of braided nylon and an accompanying sinus

Femoral Herniæ

From 108 repairs of non-strangulated femoral herniæ there were no " return " cases, and from 88 repairs of strangulated herniæ there was only 1 " return " recurrence, which was consequent on sepsis

Incisional Herniæ

There was no " return " case after 13 repairs of strangulated herniæ, but in 80 non-strangulated cases there were 7% " return " recurrences, in which the usual factors of sepsis, hæmatoma, obesity, and distension played a part It was not always clear in what manner the nylon was used in these repairs

Umbilical Herniæ (Adults Only)

There were 13% " returns " in 16 patients after strangulation and 1% in 8 patients after non-strangulation Perhaps the stretching of the years will show more returns

Discussion

MacLeod (1955) has clearly shown that excision of the sac either alone or with the addition of repair of the fascia transversalis is insufficient to give a lasting repair Most operators who have analysed their results, or studied those of others, are convinced that some form of repair is necessary

The Bassini and the overlapping repairs with catgut which hope to unit the muscle to aponeuroses often succeed because the sac has been excised and the muscles of the canal are fairly satisfactory But in too many the repair lasts only as long as the initial fibrosis induced by the catgut, and, when Nature removes in time most of the fibrosis, the thin remaining area of fibrous tissue and the muscles, which were stretched to allow approximation, give way

Tanner (1942) says that an aid to any such repair is the relaxing of the muscle by an incision in the rectus sheath When such repairs, either alone or with relaxing incisions, are accompanied by wide-biting and loosely applied unabsorbable sutures they become virtually a darn of interrupted stitches, and what virtue has been largely attributed to the relaxing incision may really be due to the presence of the unabsorbable sutures

The inclusion of some additional substance, be it heterogeneous or homogeneous, seems to aid a repair Most substances have been used to stem insistent bulging of the peritoneal cavity fabric materials, including silk, cotton, and linen, metals, including silver, gold, steel, and tantalum, and plastics, including nylon, polyethylene, and 'Terylene' The homogeneous tissues of skin, fascia, peritoneal sac, and even bone have been included in the repairs, but the repair should be possible without resort to bone-grafts or, as recently reported, diced costal-cartilage graft

Douglas (1949) has shown that silk, cotton, and linen are all mostly absorbed by the tissues and lose their tensile strength to a great extent or completely after a stay in the tissues of 6 months Of the metals, gold adds to the expense but, if properly tested, might prove just the thing for those who can afford it, and silver effects a good repair, as Cole (1941) has shown, though it irritates the tissues and does not always stand up well to sepsis Tantalum as a braided metal is difficult to use and becomes fragmented, as Ascroft (1952) has shown Stainless steel is undoubtedly the best and least irritating of the metals, and has been advocated by Abel and Hunt (1948) It may cause a sinus when used in abdominal-wall incisions and may give trouble occasionally from broken ends Mr Abel, who has used it in the repair of abdominal wounds and herniæ for 10 years, tells me he has occasionally had "broken-end" trouble in the repair of ventral incisions but has not had a sinus or "broken-end" trouble in the repair of an inguinal hernia In his careful and capable hands the darn with steel has shown only 1 "return" case. Shouldice (1953) and Ryan (1953) have latterly used steel but have not yet produced a long-term study of cases in which steel alone has been used

All available homogeneous tissues have been used Skin gives occasional dermoid-cystic troubles, is tedious to handle, and is not especially notable in producing a low recurrence-rate Most surgeons have stopped damaging the thigh to secure fascia to repair the abdominal wall The McArthur operation will provide, some have argued, enough fascia for a repair in those patients in whom no repair is necessary, and, for the repair of large herniæ in the inguinal region and for ventral and femoral herniæ, the external oblique fascia does not provide a sufficiency of strips Some doubt the permanency of fascia, and a study of the results with fascia has not shown an outstandingly low recurrence-rate

My general impression about the repair of herniæ is much the same as is the engineer's about the problem of containing stresses—that the concrete of fibrosis is more liable to fracture and give way under stress than is a reinforced concrete of fibrosis plus an included permanent framework

So long as the sutures of a darn are laid loosely they will act as a reinforcement in this way The tissues stand up well to short-acting intermittent stresses and pressures, as the soles of the feet illustrate, and the untaut sutures of a darn will not cut out of their fibrous tunnels so long as the strains are not continuous, which is not more likely to happen to the inguinal region than to the palms and soles

After comparing these present results with others published I believe that the non-porous, pliant, and permanent plastic is better than the porous and impermanent silk, and is equal to, and may be better than, the more tedious, rigid, and fragmenting steel

The persistent sinus calling for suture-removal needs comment. It may occur with any substance introduced into the tissues, even with the patient's own tissues after sepsis But a persistent sinus must be regarded as only one complication after a hernia operation and as something less than the complete failure of recurrence In the case of a repair with monofilamentous nylon it is a complication easily put right, sometimes in the outpatient department with a hook or forceps Since granulation and healing can go on around nylon sutures, any sinus should not be disturbed for at least 2 months

Of the 4 instances of persistent sinuses from which it was necessary to remove monofilamentous nylon the cause in 2 was that the layer used to suture the external oblique had worked free owing to sepsis and lay in an abscess cavity, the underlying darns being intact, wherefore they were not disturbed, in the 3rd instance a hæmatoma of the wound had caused the whole darn to become loose and lie in an abscess cavity (a case described earlier), and in the 4th instance thread as well as nylon had been used in the darn, and which suture was chiefly responsible was not clear, because the whole of the disturbed tissue was excised in one block These sources of trouble were countered as follows since the external oblique aponeurosis does not add any strength to a repair except in an overlapping procedure, shown by the way in which interstitial herniæ bulge freely beneath an intact external oblique, I now suture this layer with catgut which, if it causes a sinus, usually comes away sooner than does nylon, a large hæmatoma, which can destroy any repair, calls for no further comment, and it is probably preferable to darn with one material at a time

In my total experience over 12 years with monofilamentous nylon in the repair of herniæ, in public and in private patients, I have found it necessary to remove the whole darn, in addition to the case of hæmatoma cited above, once for an inguinal hernia and once for a femoral hernia Neither of the latter recurred.

If the recurrence-rate in my own series of inguinal repairs by a nylon darn (0 8%) is added to the rate of sinuses after monofilamentous repairs for the general series (0 4%), the total failure-rate is 1 2%, which is as good, if not better, for a 5-year figure as any result by any other material or method that I can trace

Brief Technical Details

Shaving of the hair but no other preparation until the time of operation. Iodine skin antiseptic, removed by spirit to stop a rash Skin-crease incision, one medially placed crease incision for bilateral repairs After sac excision the cremaster muscle is not sutured Plication only of the bulge in the lesser direct herniæ. Repair of the fascia transversalis at the neck of the cord in direct and indirect herniæ and at the orifice of a direct hernia

The darn is made with no 7 in two layers, either in parallel lines or in stay-lacing fashion or any pattern desired, so long as no large gaps remain. Details are given by Moloney et al (1948), who set out the requirements for any darn or lattice.

The external oblique, for reasons given earlier, and because it plays no part in the strength of the repair, and because nylon in the external oblique aponeurosis is readily palpable in the tissues though not in the darn beneath the external oblique, is closed with catgut The fat is closed with fine nylon or with fine catgut, and the skin by your own favoured method, my own being clips

Femoral herniæ are repaired from below where possible by a J-shaped needle carrying no 7 nylon, 3 or 4 sutures being inserted through Cooper's and Poupart's ligaments The medial sutures are tied firmly, but the lateral ones are tied loosely because the femoral vein must not be occluded When the darning is done from above, the inguinal canal is also darned

Ventral herniæ are repaired by cutting away all the fibrous tissues of the sac until one reaches the sound edges of the aponeurosis These are approximated in the usual way with over-and-over stitches, and a darn is laid on top of the first layer, the sutures being carried out wide of the main suture line

My usual practice after operation is to get the patient up on the same day if the operation is done early that day, otherwise the next day The patient may go home from the 3rd day onwards, depending on personal needs, but the usual time for discharge is 5–7 days, the " hospice " aspect of " hospital " not being entirely overlooked I do not order routine physiotherapy, using it mostly where special needs dictate, though many of my patients are included in the mass ward-drill for postoperative patients

The patient may do light work as soon as he feels like it, usually 2 weeks after operation, and 1 month after operation he may do any work or join a weight-lifting club

Summary

A personal series of 253 inguinal herniæ repaired with a nylon darn and surveyed more than 5 years after the last operation, with a 76% follow-up, revealed 2 recurrences (0 8%)

A series of 2181 abdominal herniæ repaired with nylon sutures by the general surgeons and their staff in the Radcliffe Infirmary and Churchill Hospital in Oxford have been reviewed from the aspects of sepsis (immediate and delayed), sinuses, hæmatomata, and " returns " with recurrence

Both monofilamentous and braided nylon were used, each in about 1000 instances, with no apparent difference in the soundness of the resulting repairs

Both varieties of nylon reacted well to immediate sepsis and needed removal for that reason in only 1 in 1000 repairs, for each variety

Both varieties showed about the same number of sinuses after sepsis and hæmatomata (21 braided, 19 monofilamentous), but the subsequent healing differed considerably With braided nylon the 21 sinuses required removal of the nylon in 17 instances, whereas with the monofilamentous nylon 19 sinuses required removal of sutures in only 4 instances

The cause of many of the sinuses and of the need for removal of the nylon was a delayed reaction seen almost entirely with the braided variety (in inguinal and femoral herniæ only, 10 braided to 1 (?) monofilamentous), which comes on 1–18 months after the insertion of the sutures and may be more of a foreign-body reaction than sepsis

" Return " recurrences for the different varieties of abdominal herniæ are analysed

A darn of monofilamentous nylon is easy to insert at operation, reacts well to primary sepsis, has a negligible " delayed " reaction, provides a sounder and more permanent repair than most, being bettered by none, and is recommended as a good method for all varieties of herniæ whether strangulated, non-strangulated, or recurrent

I am grateful to my general surgical colleagues, Mr D A Abernethy, Mr D C Corry, Mr A E Elliot Smith, and Mr A S Till, for allowing me to study the notes of patients who were under their care, and to the registrars and house-surgeons who did many of the 2000 repairs This study would not have been possibl without the secretarial help granted by Prof T P Kilner and paid for by the University of Oxford, and to Mrs J Piper, who gave thi invaluable secretarial aid, I am especially grateful

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PHARMACOLOGY AND MODE OF ACTION OF THE SULPHONYLUREAS IN MAN

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The hypoglycæmic action of the sulphonylureas is well established and much experience has been gained in their clinical application, but, so long as there is doubt about their mechanism of action, there will be hesitation in recommending their widespread or uncontrolled use

In the study of the action of any hypoglycæmic agent it is important to know (1) the effective range of blood levels, (2) how long an adequate level is maintained, and (3) the proportion of the body volume in which the drug is distributed

Pharmacological Studies

The blood-level of carbutamide stated to be effective is 6–8 mg per 100 ml (Quattrin et al 1956) and of tolbutamide 8–18 mg per 100 ml (Baird and Duncan

TABLE I—RATES OF FALL OF LEVELS OF CARBUTAMIDE IN BLOOD AND OF TOLBUTAMIDE IN PLASMA IN NORMAL SUBJECTS AND DIABETICS

Hours after 3 g of drug by mouth	Blood carbutamide (8 subjects) (Mg per 100 ml)	Plasma tolbutamide (6 subjects) (Mg per 100 ml)
4	14 5* (12 0–16 5)†	30 5 (20 9–33 4)
12	—	5 2 (2 2–11·0)
24	10·4 (8 8–11 6)	1·4 (0 7–3 6)
48	6 9 (5 8–9 4)	0 2 (0 0–0 9)
72	4 8 (6 6–3 6)	Nil
96	3 1 (2·0–4 7)	
Mean half life (hr)	40 0	3 5

* Mean † Range

1957) Our clinical data are in agreement with these statements The times for which adequate levels of these two sulphonylureas are maintained are shown in table I It is apparent that within 12 hours the level of tolbutamide has already passed its peak and becomes barely effective, whereas an effective level of carbutamide persists more than four times as long If such data are plotted on a semi-log scale for individual patients, the biological half-life of each drug can be estimated (fig 1) In this example the half-life of tolbutamide was about 4 hours and that of carbutamide about 33 hours

By extrapolating the straight lines shown in fig 1 to zero time the theoretical initial levels of these drugs can be derived Since the dose of each drug was 3 g, it was calculated that carbutamide and tolbutamide were diluted in 23 8 and 13 1 litres respectively at zero time This corresponds to 32% and 17 5% of the bodyweight These calculations were made on the assumption that the drugs were completely absorbed the amounts excreted during the process of absorption have been disregarded A similar volume of distribution was calculated when sodium carbutamide 0 5 g was administered intravenously to an anuric patient

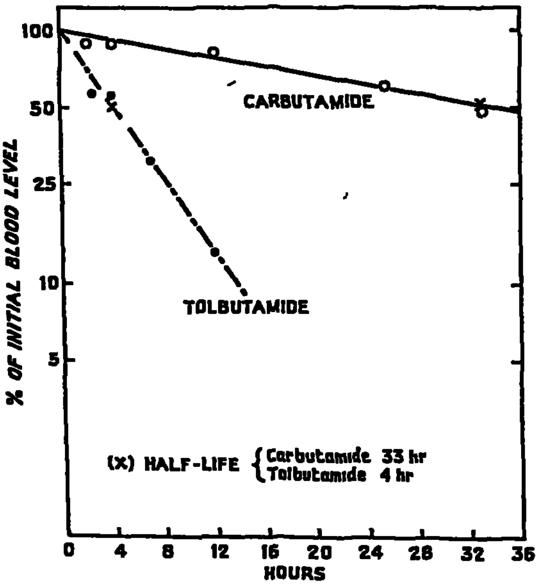

Fig 1—Rate of disposal of carbutamide and of tolbutamide from the blood

The theoretical initial level of each drug in the blood was obtained by extrapolation of the line representing the rate of decrease of the blood levels on a log scale Here the blood levels are recorded on a log percentage scale, so that the half-life can be readily assessed

Similar studies of blood-tolbutamide levels in twelve other patients showed that tolbutamide could be regarded as being distributed in a volume representing 15–25% of the bodyweight, which corresponds well to the volume of the extracellular fluid These results are in good agreement with those of Wick et al (1956) using radioactive-labelled tolbutamide in nephrectomised eviscerated rabbits and with those obtained by Quattrin et al (1956) for carbutamide

The restriction of tolbutamide to the extracellular compartment in man has been confirmed in this study by separate measurements of its levels in whole blood and plasma (table II) These results did not exclude the possibility that the drugs were preferentially concentrated in certain body tissues, such as the liver Accordingly the levels of these sulphonylureas (tolbutamide and carbutamide) in the liver and the plasma of rats were compared (table II)

TABLE II—RATIO OF TISSUE TO PLASMA LEVELS OF SULPHONYLUREAS

Sulphonylurea	Ratio $\frac{\text{Level in tissues or C.S.F. (mg. per 100 g.)}}{\text{Level in plasma (mg. per 100 ml.)}}$				
	Human erythrocytes		Rat liver		Cerebrospinal fluid
	In vivo	In vitro	In vivo	In vitro	
Tolbutamide	0 08	0 02	0 32	0 23	0 00
Carbutamide	0 02	0 02	0 27	0 12	

If the sulphonylurea had been concentrated within the liver, the ratio of the level in this tissue to that in plasma would have been greater than 1 In fact the ratios were considerably less than 1 Incubation of surviving cells (rat liver, human erythrocytes) with the drugs in vitro yielded similar results (table II)

Although tolbutamide appeared to be distributed in the extracellular fluid, the results of a single trial indicated the existence of a blood-brain barrier In this study no tolbutamide was detected in normal cerebrospinal fluid 2 hours after the administration of 2 g by mouth, when the level in the plasma was 24 mg per 100 ml

Estimations of Plasma-tolbutamide

When plasma levels of the sulphonylureas are measured, it cannot be assumed that only the therapeutically active form is being estimated In fact Quattrin et al (1956) found that up to 20% of carbutamide in human blood was in the inactive acetylated form, and, using the method described below, we have shown that 24 hours after a single oral dose of the active drug 10–28% of tolbutamide occurs in plasma as the inactive carboxylic ester

Measurement of Ratio of Carboxytolbutamide to Tolbutamide

A sample of carboxytolbutamide was prepared from several 24-hour collections of urine passed by patients receiving large doses of tolbutamide This compound was precipitated by acidifying the urine to pH 1 and allowing it to stand for 12 hours The white crystalline precipitate was filtered off and then purified by redissolving in ethanol, concentrating at room temperature, and then precipitating by seeding This was repeated twice The melting-point of the product was 215°C, which is that of carboxytolbutamide (Louis et al 1956)

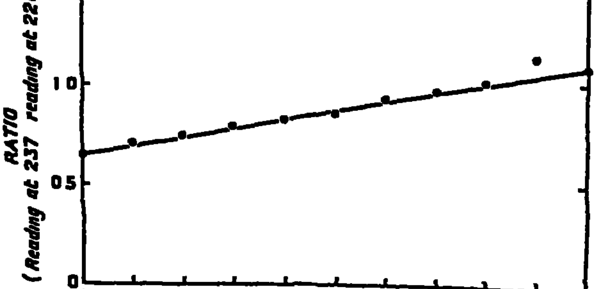

Fig 2—Proportions of tolbutamide and carboxytolbutamide in mixtures of these compounds

Ratio of readings on ultraviolet spectrophotometer at 237 mμ to those at 228 mμ are given on the ordinate, and the corresponding proportions of tolbutamide and carboxytolbutamide on the abscissæ

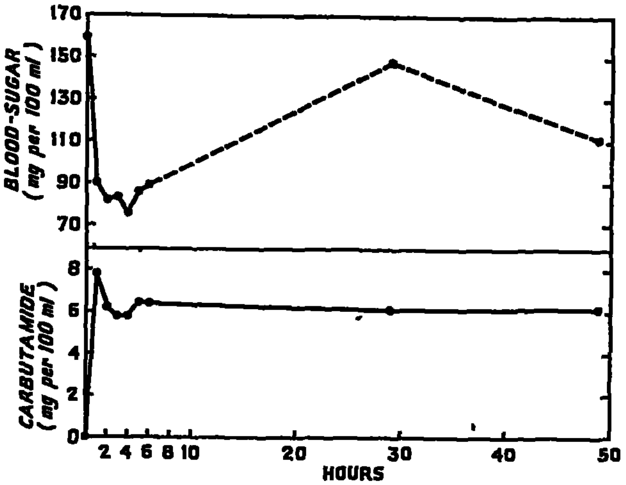

Fig 3—Levels of carbutamide and sugar in the blood of the anuric patient given sodium carbutamide 0 5 g intravenously at time 0

The maximum absorption of tolbutamide in alcohol took place at 228 mμ (measured with a 'Unicam SP 500' spectrophotometer), and that of carboxytolbutamide in alcohol at 237 mμ Equal weights of tolbutamide and of carboxytolbutamide were dissolved in identical volumes of ethanol Mixtures of these two solutions were then made in nine different proportions The spectrophotometric absorption of the mixtures and of the two pure solutions was then read at 228 and 237 mμ, and the ratio $\frac{\text{absorption at 237}}{\text{absorption at 228}}$ was then calculated for each of them

When this ratio was plotted against the proportional levels of carboxytolbutamide and of tolbutamide, a straight line was obtained (fig 2) In the case of tolbutamide alone the ratio was 0 656 and in the case of carboxytolbutamide alone it was 1 08 Intermediate ratios correspond to proportions of these two compounds which can be read off the figure In this way the proportion of carboxytolbutamide in blood and urine specimens was determined

Excretion of Tolbutamide

The plasma level of sulphonylurea depends not only on the rate of its metabolic change in the body but also on its excretion The route of excretion is probably entirely renal

This was illustrated by some observations on an anuric patient, in whom the blood level of carbutamide remained practically constant during the 50-hour observation period following intravenous injection of sodium carbutamide 0 5 g (fig 3) It proved impracticable to calculate the renal clearance of tolbutamide because of the variable blank values obtained in separate specimens of urine, the high proportion of the carboxy derivative in the urine, and an unknown proportion of tolbutamide bound to plasma-proteins Nevertheless an indirect assessment of the kidney's action on tolbutamide was obtained by following the rate of its disappearance from the plasma under a variety of circumstances affecting the kidney (table III)

In two non-diabetic patients with considerable impairment of glomerular filtration, estimated by the clearance of endogenous creatinine, there was only a small reduction in the rate of disappearance of tolbutamide from the plasma compared with the mean rate in six normal subjects On the other hand, probenecid ('Benemid'), which affects tubular transport mechanisms, slowed the rate of disappearance considerably Sodium bicarbonate 20 g did not appreciably accelerate the rate of disappearance of tolbutamide from the plasma in a single normal subject

We conclude that renal tubular transport is important in the excretion of tolbutamide, as might indeed be inferred from the fact that the proportion of tolbutamide to carboxytolbutamide is several times greater in the plasma than it is in the urine

Mode of Action

On reviewing the published work of others, there remain two plausible explanations of the mode of action of the hypoglycæmic sulphonylureas

(1) The first is that they stimulate the release of insulin from the pancreas This hypothesis accords with the fact that in pancreatectomised patients the sulphonylureas do not have a hypoglycæmic effect In fact the type of diabetic that responds best is precisely the type that does not lack insulin—as shown by plasma-insulin assays and extraction of insulin from the pancreas post mortem (Wrenshall and Best 1956) The work of Ashworth and Haist (1956), on beta-cell hyperplasia induced by the sulphonylureas, and of Loubatières (1955) and Colwell et al (1957), showing the increased efficacy of these compounds when infused into the pancreaticoduodenal artery of dogs, support this explanation Pozza et al (1956) demonstrated an increase of hypoglycæmic activity in blood containing tolbutamide perfused through the pancreas of dogs

A hypothesis with similar implications is that the main action of the hypoglycæmic agent is the inhibition of insulinase (Mirsky et al 1956), but more recent work has indicated that the blood-tolbutamide concentrations obtained in clinical practice have no anti-insulinase action (Vaughan 1956), and no effect has been noted on the rate of destruction of insulin labelled with ^{131}I (Wick et al 1957, Volk et al 1957)

(2) The second main explanation is that hypoglycæmia results from a decreased glucose output from the liver Much work supports this theory, including studies in man of the reduced conversion of fructose and galactose to glucose (Renold et al 1956), which normally takes place in the liver and direct measurements of the hepatic output of glucose by catheterisation of the hepatic vein in dogs (Anderson et al 1956, Purnell et al 1956) and man (Recant and Fischer 1957a)

The explanation offered at one time by German workers that tolbutamide inhibits the production of glucagon by the alpha-cells of the islets of Langerhans is now no longer supported by the Germans themselves (von Holt et al 1956, Ferner and Runge 1956), and it certainly does not account for the refractoriness of alloxan diabetes to the hypoglycæmic action of the sulphonylureas Most workers agree that glucagon and adrenaline still produce their typical hyperglycæmic action in the presence of these hypoglycæmic agents (Franke and Fuchs 1955)

Other hypotheses, such as those involving actions on the pituitary, adrenal, or thyroid glands (Mortimore et al 1956) or on absorption of food from the intestine (Friedlich et al 1956), or on the renal threshold for

TABLE III—RATE OF DISAPPEARANCE OF TOLBUTAMIDE FROM PLASMA IN VARIOUS CIRCUMSTANCES

	Plasma-tolbutamide (mg per 100 ml)					
Hours after ingestion of tolbutamide 3 g	Normal subjects (mean of 6)	Patient with hypertension (glomerular filtration rate 52 ml per min)	Patient with chronic nephritis (glomerular filtration-rate 38 ml per min)	Patient with gout receiving probenecid	Normal receiving probenecid	Normal receiving 20 g of NaHCO$_3$ (urine pH 7 8)
4	30 5	29 6	20 9	27 1	32 6	24 6
12	5 2	11 2	—	—	—	3·0
24	1 4	3 9	5 7	10 3	12 8	0 8
48	0 2	1·4	2 2	6 2	8·0	Nil
72	Nil	Nil	Nil	5·0	6 4	—

glucose, have failed to explain the main hypoglycæmic effect

As well as the supporting papers cited, the large literature on this subject contains much to counter each of the two main theories of the mode of action For instance, many studies have failed to produce evidence of increased utilisation of glucose (Recant and Fischer 1957b), such as would be expected from a stimulus to the production of insulin, and, on the other hand, tolbutamide has been shown to lower the blood-glucose in hepatectomised rats and dogs (Dulin and Johnston 1957)

In the absence of any single generally acceptable theory we thought it probable that more than one type of hypoglycæmic action may occur in one person The assessment of the relative importance of such hypoglycæmic mechanisms was then our main task In this it was critical to obtain evidence that the sulphonylureas have an insulin-like action which would favour the view that insulin is potentiated or its production stimulated, and it was important to try to separate an effect on the production of glucose by the liver in the fasting state from an effect on the metabolic processes of absorbed carbohydrate Studies of our clinical material, which consisted of two contrasting types of diabetics, helped to provide information on both these aspects

TABLE IV—RESULTS OF GLUCOSE-TOLERANCE TESTS WITH AND WITHOUT TOLBUTAMIDE IN STABLE DIABETES

—	Control G-T T without tolbutamide	G-T T 3 hours after administration of tolbutamide 3 g
%Fall in fasting venous blood-sugar		25 6 (15)
Mean capillary/venous blood-sugar difference (mg per 100 ml)	12 8 (13)	14 0 (15)
%Fall in serum-phosphorus	9 9 (13)	12 7 (14) p=0 4
%Fall in serum-potassium	9 6 (9)	8 1 (7)

Numerals in parentheses indicate number of persons from whom the mean was derived

Clinical Studies

GROUP 1

The first group consisted of thirteen diabetics selected because they were likely to show a good hypoglycæmic response to the sulphonylureas, and in the event each did They were older stable diabetics with no tendency to ketosis, of whom none was grossly overweight, and some were under average weight The investigation of this group was planned to seek evidence of any hypoglycæmic action attributable to the release of insulin following the administration of the initial dose of tolbutamide We, like Goetz et al (1956) and Mirsky et al (1957), considered that the initial action of tolbutamide might be mediated mainly by the release of insulin, but that, after long-continued administration, the hypoglycæmic effect was less likely to be attributable to increased production of insulin We therefore repeated the study of the effects of a test dose of tolbutamide after it had been administered continuously for several weeks or months in 4 of the patients

Method of Investigation

The trial was planned to use the diabetic patient for bioassay of insulin by measuring changes which could be regarded as typical of the known actions of the hormone (1) an increased difference between capillary and venous blood sugar levels (method of Nelson 1944, Somogyi 1945), (2) a fall in the level of inorganic phosphorus in the serum (method of Fiske and Subbarow 1925), and (3) a fall in the serum potassium level (Internal Standard flame photometer) during an oral glucose-tolerance test Control data were obtained by measuring these changes in the patient while on no treatment during a glucose-tolerance test lasting 2½ hours after the administration of glucose 50 g by mouth The test data were obtained by repeating the procedure 3 hours after tolbutamide 3 g had been given by mouth The six samples of venous blood obtained in each case were collected, when feasible, without using a tourniquet, and both venous and capillary blood-sugar levels were estimated in duplicate Care was taken to avoid hæmolysis in the specimens used for estimating inorganic phosphorus and potassium

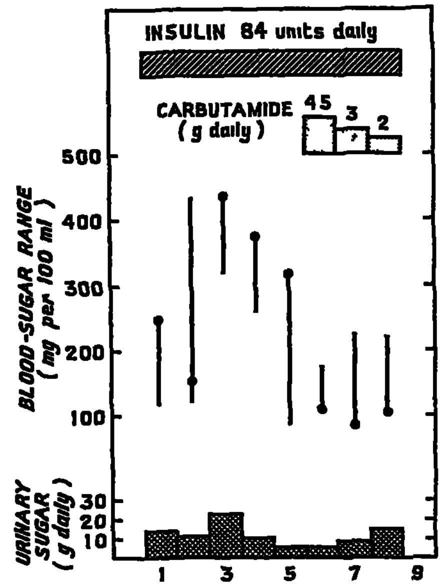

Fig 4—Response of blood-sugar, measured at three different times of the day, to carbutamide in a "brittle" diabetic

Blood-sugar levels were measured fasting (●), 3 hr after lunch, and 2 hr after supper On treatment with carbutamide the fasting blood-sugar, previously the highest in the daily range, became the lowest Patient was a man, aged 25 and weighing 55 kg, on a 2000-calorie diet

Results

The results are shown in table IV The mean fall in the

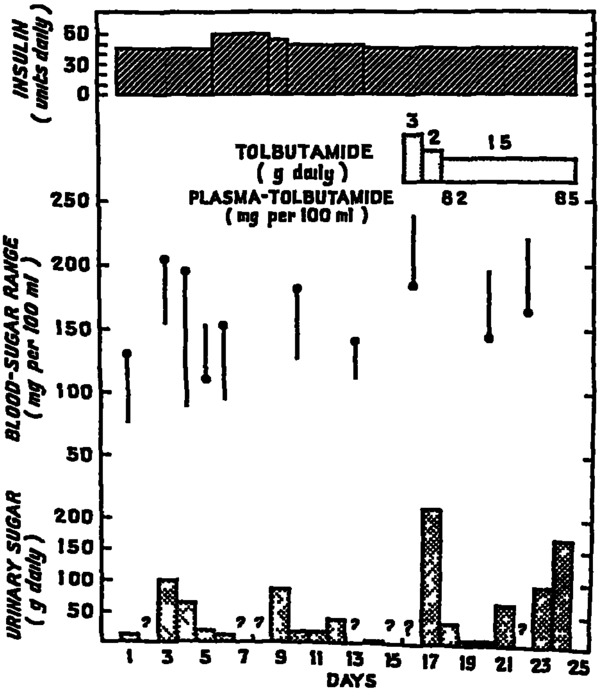

Fig 5—Response of another "brittle" diabetic to tolbutamide

Here too the fasting blood-sugar (●) became the lowest in the daily range during the administration of tolbutamide, although previously the fasting blood-sugar level was usually highest in the daily range Patient was a man, aged 43 and weighing 54 5 kg, on a 2000-calorie diet.

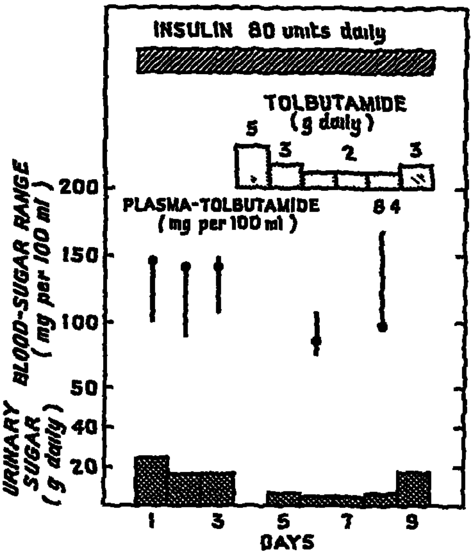

Fig 6—Response of "brittle" diabetes to tolbutamide shown by fasting blood-sugar level (●) in a woman, aged 31 and weighing 43 8 kg, on a 2200-calorie diet

fasting venous blood-sugar level 3 hours after administration of tolbutamide 3 g, compared with that on the day of the control glucose-tolerance test, was 25 6% The remaining data can be used to indicate whether this fall was due to the action of endogenous insulin Thus the mean difference between capillary and venous blood-sugar levels in specimens drawn on six occasions in each glucose-tolerance test was 12 8 mg per 100 ml in the control glucose-tolerance tests and 14 mg per 100 ml in the tolbutamide glucose-tolerance tests The capillary/venous difference in the control test suggests that these diabetics did not totally lack insulin, but tolbutamide did not significantly increase the difference between capillary and venous blood-sugar levels as would have been expected with increased action of insulin at the periphery The lack of any significant increase in the fall of serum-inorganic-phosphorus after administration of tolbutamide (12 7% compared with 9 9% in the control, $p=0\ 4$) also shows no evidence of any increased action of insulin at the periphery The failure to find any significant increase in the fall of serum-potassium after administration of tolbutamide is in keeping with the other data indicating no increase of insulin effect

Studies on these stable diabetics confirmed that the main action of tolbutamide was on the fasting blood-sugar level. The shape of the glucose-tolerance curves and the timing of the fall of serum-inorganic-phosphorus and serum-potassium were not affected Plasma-tolbutamide levels obtained during the tests were as high as 32 mg per 100 ml When the tolbutamide-tolerance test was repeated after several weeks or up to more than 2 months in four patients, the fasting venous blood-sugar level was even lower than in the first tolbutamide test, but there was no tendency towards greater capillary/venous blood-sugar differences or a greater fall in serum-inorganic-phosphorus

GROUP 2

The second group consisted of fifteen diabetics selected because they were typically unstable or "brittle" They were known to show wide variations between ketosis and hypoglycæmia and were all young or middle-aged adults None was obese The daily insulin dosage extended from 48 to 124 units (mean 78 units) in different patients Six of the fifteen had renal glycosuria, the renal threshold for sugar being about 140 mg per 100 ml or lower This had doubtless contributed to the brittleness of the diabetes because of the tendency to assess insulin dosage on qualitative tests for urinary sugar

The study was designed to answer the following questions (1) Would the sulphonylureas decrease the requirement for insulin? (2) Would they make the diabetes more stable? (3) Would brittle diabetes react differently from mild stable diabetes?

Method of Investigation

All except two of the fifteen were admitted to the ward but were ambulant They were given a diet of constant calorie value and then stabilised on insulin alone Capillary blood-sugar levels were measured in duplicate by the Nelson-Somogyi method at 8 A.M, 4 P.M, and 8 P.M for a control period of 3 to 20 days The times at which blood samples were collected represented fasting, 3 hours after lunch, and 2 hours after supper Total daily sugar excretions were measured (Somogyi 1941) Carbutamide or tolbutamide was then added to the regime in two daily doses The quantity given was usually 3 g on the first day, 2 g on the second day, and then 1–2 g daily for maintenance The estimations of sugar in the blood and in the urine were then continued for 3 to 16 days These results were then compared with those obtained in the control period

Results

Although many of the patients were well balanced in the control period, with blood-sugar levels within the normal non-diabetic range, in no case did carbutamide or tolbutamide, when added to the regime, induce clinical hypoglycæmia The blood-sugar levels were not in fact significantly lower when

TABLE V—BLOOD-SUGAR LEVELS BEFORE AND DURING SULPHONYLUREA THERAPY IN BRITTLE DIABETES

Case no	Calories in diet	Dose of insulin (units)	Time of test	Control		*Carbutamide*	
				Blood-sugar (mg per 100 ml)	*S.D*	Blood sugar (mg per 100 ml)	*S D*
1	1800	80	8 A M	174 (7)	66·0	110 (5)	46 0
			4 P M	108 (6)	58·0	114 (5)	34 5
			8 P.M	136 (6)	62 0	138 (5)	62 0
2	2500	84	8 A M	307 (5)	99 0	99 (3)	11·5
			4 P M	182 (5)	101 5	169 (3)	37·0
			8 P M	251 (5)	135 5	203 (3)	24·0
3	1800	56	8 A.M	122 (3)	49 0	166 (5)	31·0
			4 P M	139 (2)		148 (3)	13 0
			8 P M	178 (3)	35 0	194 (3)	18·0
						Tolbutamide	
4	2000	48	8 A.M	170 (6)	28 0	163 (3)	16·0
			4 P M	128 (4)	32 0	183 (3)	10 5
			8 P M	132 (5)	16·0	217 (3)	18·0
5	2700	124	8 A.M	129 (4)	30 0	117 (3)	21·0
			4 P M	122 (3)	29 0	106 (3)	11·0
			8 P M	171 (3)	42 0	161 (3)	17 0
6	2000	80	8 A.M	94 (3)	16·0	91 (4)	8·0
			3 P M	109 (4)	20 5	90 (4)	11·0
			8 P M	124 (4)	16·0	115 (4)	12·0
7	1600	48	8 A M	253 (2)		185 (9)	36·0
			3 P M	159 (4)	40 0	168 (7)	26 0
			8 P.M	217 (6)	48 5	216 (8)	37·0
8	1800	110	8 A M	89 (3)	10 5	96 (3)	6·0
			4 P M	109 (3)	37 0	109 (3)	5·0
			8 P M	120 (2)		119 (3)	13·0
9	2000	56	10 30 A M	115 (6)	28·0	127 (20)	33·0
			3 30 P M	114 (6)	23·0	128 (16)	35·0

Numerals in parentheses indicate number of determinations used in calculating mean these hypoglycæmic agents were given, except for the fasting blood-sugar level in six of the eleven cases in which suitable data were obtained Three such cases are illustrated in figs 4–6 Some patients had their lowest blood-sugar at 8 A M in the control period and thus could not show the sort of change illustrated in these three figures Since the fasting blood-sugar level of a diabetic is determined by the hepatic glucose output, we conclude that carbutamide and tolbutamide lowered the fasting blood-sugar level in some of these brittle diabetics by significantly decreasing the output of glucose from the liver

The stability of nine of these diabetics has been analysed by comparing the standard deviations from the mean blood-sugar levels at three different times in the day in the control period and when receiving carbutamide or tolbutamide The results are shown in table V There was a decrease in the standard deviation from the mean blood-sugar level at each of the three different times in the day when taking the hypoglycæmic agent except in one patient, and no significant change at one of the three times in one other patient It is concluded that tolbutamide and carbutamide lessened the variations in blood-sugar levels in eight of nine of these brittle diabetics, and this happened not only in the fasting state but also in the 2-hour and 3-hour postprandial states In only one instance did this increased stability offer any easily apparent clinical advantage.

The daily excretions of sugar, compared with the corresponding blood-sugar levels, do not suggest that tolbutamide and carbutamide significantly altered the renal threshold for glucose No toxic effects of any kind were seen in these groups of diabetics during treatment

Conclusions

Since administered insulin was not rendered more effective by carbutamide or tolbutamide, except possibly in the fasting state, we think it unlikely that these drugs inhibited the destruction of the insulin given The results are consistent with the theory that the drugs inhibited output of glucose by the liver Although the brittle diabetics were not of the type usually thought to respond to the sulphonylureas, and fell indeed into the category of diabetics probably lacking insulin of their own, nevertheless both carbutamide and tolbutamide lowered the fasting blood-sugar in six out of eleven patients and decreased the variations in blood-sugar levels in eight out of nine These actions are therefore unlikely to be attributable to any stimulus to production of insulin

In conclusion, sulphonylureas appear to decrease to an important extent the hepatic output of glucose in both stable and the contrasting unstable diabetics Our data do not exclude the possibility of a stimulus to the secretion of insulin, particularly if sulphonylureas were to have more effect on the action of insulin on the liver than elsewhere, as has been suggested by Frawley et al (1957), but our data did not yield evidence to support this

Summary

Tolbutamide was distributed in a volume corresponding to 15–25% of the bodyweight, equivalent to the extracellular fluid, and carbutamide had about double this volume of distribution

Carbutamide persisted in the body more than four times as long as tolbutamide, which should therefore be given at least twice a day

Up to 28% of “ tolbutamide ” estimated in plasma was found to be in the form of its physiologically inactive carboxylic ester

Clinical studies of the kidney’s action on tolbutamide are reported

Explanations of the mode of action of the sulphonylureas are reviewed briefly, and studies of their action in a group of stable and a group of unstable diabetics are reported

We conclude that the sulphonylureas significantly reduced the output of glucose from the liver in both groups of diabetics and that they decreased the variation in the blood-sugar of most of the unstable ones

No evidence of increased secretion of insulin was obtained

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THE FŒTAL LOSS IN PREGNANCY TOXÆMIA

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Though pregnancy toxæmia still carries a serious risk for the mother, we can now, without increasing that risk, give more consideration to the fate of the baby The loss of child life from this cause remains very great

In a review of 819 cases of toxæmia in the hospital for the past five years it has proved quite easy to separate out 72 in which stillbirth or neonatal death was mainly or entirely due to the toxæmic process Clinically these fell into four groups

Group 1 intrauterine death.
Group 2 accidental hæmorrhage
Group 3 intrapartum death
Group 4 neonatal death

“ Intrauterine death ” includes only death of the fœtus in utero before the onset of labour and not as a result of accidental hæmorrhage

Table I shows the numerical distribution in these groups This simple breakdown brings out the importance

TABLE I—LOSS OF FŒTUS IN PREGNANCY TOXÆMIA

Group 1 intrauterine death	Group 2 accidental hæmorrhage	Group 3 intrapartum death	Group 4 neonatal death	Total
29 (*40%*)	19 (*26%*)	14 (*19·4%*)	10 (*14%*)	72

of intrauterine death which forms the largest single group In their much bigger series Hamilton, Jeffcoate, and Lister (1949) found that the same proportion of the total fœtal loss lay in this group

Groups 1 and 2 not only are the largest numerically but also seem likely to have common lethal factors with groups 3 and 4 In a previous review of intrapartum fœtal death FitzGerald and McFarlane (1955) found that toxæmia did not show as great an effect as was expected In the present series the considerable incidence of antepartum death suggests that this may be due to the removal of potential cases from the field before labour begins

The greater incidence of intrauterine death in primigravidæ and of accidental hæmorrhage in multigravidæ is well recognised (table II)

Table III roughly indicates the efficacy of orthodox hospital treatment, it suggests that this is more successful in the avoidance of accidental hæmorrhages than in the prevention of intrauterine death, for in the latter group there is little difference between the booked and the non-booked cases

TABLE II—EFFECT OF PARITY ON FŒTAL LOSS IN PREGNANCY TOXÆMIA

—	Total	Intrauterine death	Accidental hæmorrhage	—
Primigravidæ	43	45%	19%	Percentage of total primigravid loss
Multigravidæ	29	34%	41%	Percentage of total multigravid loss

Birthweights

An important contrast between these two groups of fœtal deaths is provided by a study of the birthweights It is well recognised that the children of toxæmic mothers tend to be small, but the importance of this observation has been obscured by consideration of the birthweight in relation to an artificial prematurity standard of 5¹/₂ lb We suggest that the important relationship is that between the birthweight and some reasonable standard of what the weight should be at that particular stage of gestation This should give a realistic picture of any stunting of fœtal growth as a result of the toxæmia Recently Baird et al (1957) have pointed out the type of case where fœtal growth is retarded and intrauterine death takes place

Figs 1 and 2 show the birthweights in cases of intrauterine death and accidental hæmorrhage, and fig 3 shows curves obtained from these diagrams superimposed on a curve of normal fœtal weights at varying gestation periods, obtained from the work of Clatworthy and Anderson (1944) which was based on the studies of Streeter (1920) Fig 3 shows clearly that it is the cases of intrauterine death which are most affected by this stunting of fœtal growth, the curve of accidental hæmorrhage approximates much more closely to the normal, the curves actually meeting at 35 weeks' gestation

TABLE III—EFFECT OF TREATMENT

—	Total	Intrauterine death	Accidental hæmorrhage	—
Booked	39	38%	10 8%	Percentage of total booked loss
Non-booked	33	44%	40%	Percentage of total non-booked loss

From a consideration of these points the suggestion emerges that there are two different ways in which fœtal death takes place in pregnancy toxæmia In one group growth is diminished or ceases and the baby " fades out " as an intrauterine death without any clearcut exacerbation of the toxæmia, presumably as a result of failure to obtain sufficient oxygen or nutrients In the other group placental function remains more or less adequate, allowing more normal fœtal growth, until there is an abrupt interference with the oxygen supply by the stripping of the placenta from its bed by hæmorrhage

It is now established that, in many cases of pregnancy toxæmia, there is a defective blood-supply to the placental bed owing to spasm of the arteries supplying the uterus This would explain intrauterine death associated with stunting of fœtal growth May it not be that in other cases this spasm of the uterine arteries is absent or diminished, thus permitting normal nutrition and growth of the fœtus but allowing the effects of the generalised hypertension to be transmitted to the vessels supplying the placental bed, with resultant retroplacental hæmorrhage in a proportion of cases? The existence of the two types of case—i e, with and without spasm of the uterine arteries, is supported by the atypical results obtained in some of the cases investigated with radioactive isotopes for the efficiency of the uterine circulation in toxæmia, and by similar discrepancies in cases of toxæmia where the placental function has been deduced from its output of hormones (Russell 1957)

Perhaps the most graphic illustration is seen in two toxæmic cases examined for adequacy of placental function by Clayton et al (1956) using radiosodium and a scintillometer In one case intrauterine death took place at 34 weeks with the delivery of a fœtus weighing 2 lb 13 oz The uptake of radiosodium, indicating " placental efficiency," was grossly deficient in three estimates shortly before the fœtus died By contrast, in a second case, the patient showed fairly severe toxæmia at 39 weeks, but placental function estimated at this time showed little change from normal

Treatment

Any considerable improvement in treatment may be impossible until more is known about the cause of the toxæmia Meanwhile advances can come only from better application of present methods

Dieckmann and Brown (1939) formulated a general principle of treatment as follows

> " Over 60% of the fœtal and neonatal mortality in toxæmia patients occurred with the fœtuses weighing 1,000 to 2,000 grams Since maternal toxæmia has no further effect on the fœtus once it is born the treatment of the mother should be directed to prolonging the pregnancy as long as it is compatible with her best interests to obtain as old and as heavy a baby as possible "

This principle usually leads to the attempt to maintain the pregnancy until the 37th week of gestation, and the success of this policy must depend on the avoidance of accidental hæmorrhage and intrauterine death during that time The results in the present series suggest that, though it is to some extent successful in preventing accidental hæmorrhage, it does little to prevent failure of fœtal growth followed by death in utero

Again, if this policy of waiting is to succeed, there must be some reasonable warning if and when fœtal growth

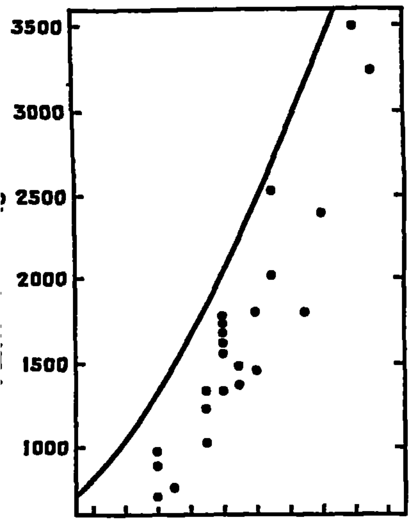

Fig 1—Birthweights in intrauterine deaths, and curve of normal growth

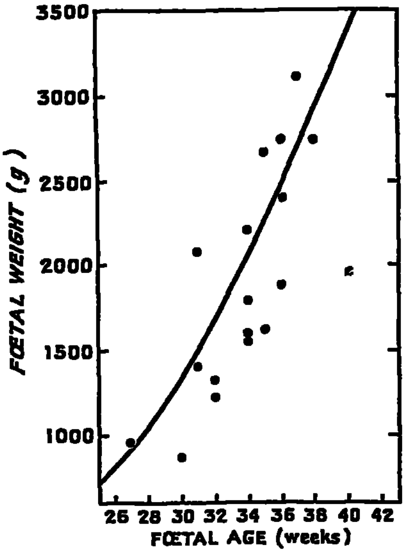

Fig 2—Birthweights in accidental hæmorrhage, and curve of normal growth

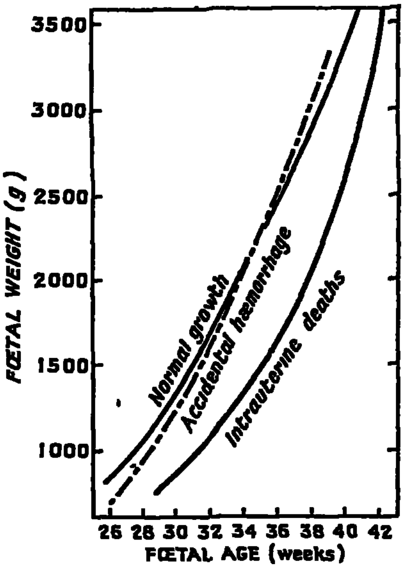

Fig 3—Comparison of figs 1 and 2 with normal fœtal weights

is failing Examination of case-records does not reveal any consistent signs of worsening of the toxæmia The records bring out the great importance of noting evidence of failure of fœtal growth in those cases which terminated in death in utero, and show that insufficient attention had been paid to these signs References to the importance of this clinical observation are not very common Townsend (1955) emphasised this point, and other workers agreed with him

The failure of fœtal growth may be recognised by the observation that the height of the fundus is much below that expected from the history If a more careful watch is kept, it should be possible to note the failure of the fundus to rise in successive weeks In 19 of the 29 cases of intrauterine death considered here the fundus was noted as distinctly low for the dates, and in 5 cases failure to enlarge was noted In 3 cases where X-ray examination for maturity was undertaken, there appeared to be an associated delay in the appearance of the ossification centres This might lead to a mistaken rejection of the patient's last menstrual period as a basis for calculation

It has been suggested that the presence or absence of albuminuria may be of special significance in differentiating cases in which intrauterine death is likely, but this is doubtful Albuminuria was present in 26 of the 29 cases of intrauterine death and in 16 of the 19 cases of accidental hæmorrhage The presence of albuminuria would therefore not assist in indicating which form of trouble might be anticipated 109 babies born alive of toxæmic mothers weighed less than $5^{1}/_{2}$ lb, only 13 of these had a normal birthweight relative to maturity, and 10 had albuminuria Of the 86 babies with a low birthweight relative to maturity 25 had no albuminuria These figures show that albuminuria is no reliable guide to those babies who are stunted in growth

Fig 4 shows the times of occurrence of accidental hæmorrhage and of intrauterine death, nearly 90% of the former and 70% of the latter occurred before the 37th week of gestation Obviously it cannot be argued that earlier induction would save all these babies, for some would then be lost from prematurity and the hazards of induction Nevertheless these results suggest caution in the policy of allowing the pregnancy to proceed, particularly if there is evidence of failure to grow Hamilton et al (1949) found results curiously little influenced by methods of delivery, but the timing seems to be of even greater significance than the method These authors also found that cæsarean section offered the best chance of survival to babies weighing less than 4 lb, and we believe that this applies particularly to the small starvelings of toxæmia

The following brief case-reports illustrate how treatment, where there is failure of fœtal growth, may be influenced by these various considerations

Case 1 —Mrs A, aged 29, primigravida, had taken four years to conceive She was seen as a consultation at the 32nd week Blood-pressure 170/100 mm Hg, urine clear, fundus uteri at 24 weeks' level She was admitted forthwith rest and reserpine stablised her blood-pressure at about 150/90, with a trace of albuminuria intermittently The patient was quite sure of her menstrual dates, but ten days before the expected date of delivery based on them the fundus was at the level of only 32 weeks Radiography showed fœtal development equal to that of 30 weeks' maturity, so the pregnancy was allowed to continue to await further growth of the fœtus Nine days

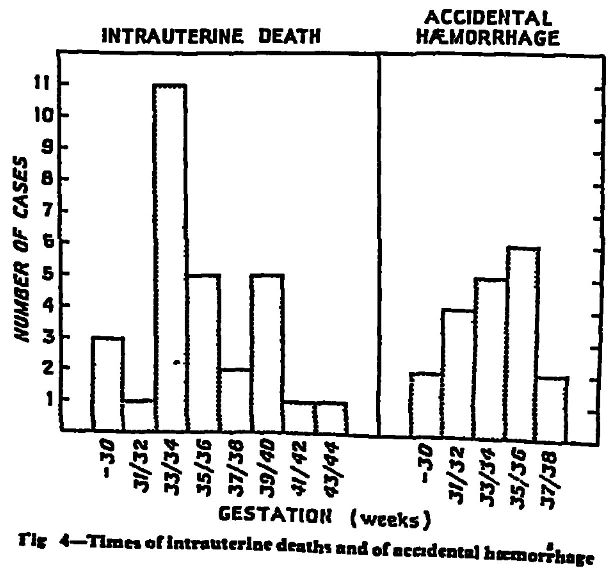

Fig 4—Times of intrauterine deaths and of accidental hæmorrhage

later the fœtal heart sounds disappeared, and six days after this a macerated infant weighing 4 lb was delivered, the placenta weighed 13 oz

This delivery took place about two months after admission to hospital, and there had been ample opportunity to deliver a live child

Case 2 —Mrs B , aged 36, had had one miscarriage previously and had been wanting a baby for eleven years She was a booked case with essential hypertension admitted at 36 weeks after her last menstrual period because of continuing mild hypertension with sudden increase of weight and œdema The level of the fundus was that of a 32 weeks' gestation and X-ray examination at this time suggested 32 weeks' maturity The blood-pressure was stabilised at 140/90, with a slight trace of albumin on two occasions only About a week after admission the fœtal heart showed some irregularity and tachycardia, and in view of this and the failure of the baby to grow a cæsarean section was performed in the 38th week of gestation, reckoning from the patient's last menstrual period, of which she was quite confident A living child weighing 4 lb 11 oz was delivered and survived satisfactorily

This patient occupied the next bed to that of case 1, and the first tragedy undoubtedly influenced the more active policy in this case

Case 3 —Mrs C , aged 43, primigravida, was admitted as an emergency with severe toxæmia, blood-pressure 160/100 and heavy albuminuria at the 39th week of gestation, the level of the uterine fundus was that of 32 weeks After twenty-four hours' rest and heavy sedation cæsarean section was performed and a small "starveling" baby was delivered weighing 3 lb 11 oz Radiography of the baby seven days after delivery showed a fairly well developed astragalus but no epiphysis at the lower end of the femur, so the age appeared to be between 33 and 35 weeks

Once again the radiological evidence clashed with that of the patient's menstrual dates The infant gave rise to considerable anxiety at first, but survived satisfactorily It is very doubtful if this would have been the result if an attempt had been made to hold off delivery to allow further growth of the child

Summary

The chief causes of fœtal loss in toxæmia are accidental hæmorrhage and intrauterine death before labour

Evidence is produced suggesting that whereas in some cases placental function remains adequate allowing fairly normal fœtal growth until there is a retroplacental hæmorrhage, in others the fœtus "fades out" because spasm of the uterine arteries reduces its supply of oxygen or nutrients

Provided accidental hæmorrhage can be avoided, the policy of maintaining pregnancy till the 37th week may be successful in the first group of cases, but it is unsuccessful for those in which failure of fœtal growth is followed by death in utero

A close watch should be kept for evidence that the fœtus is not enlarging normally

The timing of delivery may be of more importance than the method

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ORIGIN OF PERIPHERAL TUBERCULOUS LYMPHADENITIS IN CHILDHOOD

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The relation of peripheral tuberculous lymphadenitis to primary tuberculous infection is still a matter of discussion and comment (American Trudeau Society 1954) Though mediastinal or mesenteric tuberculous lymphadenitis is usually accepted as evidence of a primary infection in the respective drainage area, this is not true of inguinal or preauricular adenitis and not always of cervical adenitis

We became interested in the origin of peripheral tuberculous lymphadenitis, and its relation to the primary tuberculous infection, while we were studying the recognition of primary foci in the skin or mucous surfaces (Miller 1953) and the natural history of the related tuberculous lymphadenitis (Miller and Cashman 1955a) With the experience gained in this and other studies we thought we could usefully review all the children seen in our department from 1947 to 1952 who had been diagnosed and treated as having peripheral tuberculous lymphadenitis

We asked this question Is peripheral tuberculous lymphadenitis, wherever it presents, likely to be part of a primary complex, or does it arise by hæmatogenous spread from a primary focus in the lung or alimentary tract ?

Children Studied

Between 1947 and 1952, tuberculous infection in a group of superficial glands was diagnosed in 338 children Coming in the ordinary course of clinical work, the children were seen at all stages of the tuberculous infection and only those with a visible primary focus were studied initially as a special group Of these we excluded all who had not had a complete radiological examination (neck, chest, and abdomen) when first seen, and all who could not be traced for a second radiological and clinical examination at least two years afterwards This radiological examination was necessary to judge the probable duration of infection in the glands We were left, therefore, with a group of 163 children, of all ages to 15 years, known to have tuberculosis, who had radiological records in addition to clinical notes and were examined again at least two years after they presented at hospital The diagnosis remained in doubt in only 6 children, who had a positive tuberculin skin test and enlarged glands which neither softened nor calcified

We have previously shown that

> In children with recent tuberculous infection of the inguinal, axillary, or cervical glands (except the tonsillar), careful examination will sometimes reveal a primary focus on the skin or mucous surface drained by the glands (Miller 1953)
>
> The primary focus usually leaves a characteristic scar, but in certain circumstances may disappear without trace (Boyes, Jones, and Miller 1956)
>
> The peripheral glands draining a primary focus on skin or mucous membrane usually show radiological calcification within two or three years of infection In most cases, this calcification is the only residual sign of tuberculous infection

THE ANATOMICAL DISTRIBUTION IN, AND THE CLINICAL GROUPING OF, 163 CASES OF PERIPHERAL TUBERCULOUS LYMPHADENITIS

Group of lymph-glands involved	Children with a known time of infection—all with unilateral gland enlargement					Children without known time of infection					
						Unilateral					
	Visible primary focus	Tuberculin conversion observed	Tuberculin conversion under 1 yr of age	Conversion with erythema nodosum	Conversion with "fever" of onset	Without calcification when first seen	With calcification when first seen	Glands showing calcification without abscess formation	Bilateral enlargement	Cases of special interest	Total
Preauricular	10									1	11
Postauricular	1										1
Occipital	1										1
Submental	3										3
Supramandibular	1										1
Axillary	3									1	4
Epitrochlear										2	2
Inguinal	13								*1	1	15
"Supraclavicular"				1		1	2		1	2	7
Tonsillar	9	4	7	3	10	26	26	9	16	2	118
Submandibular	6										
Total	47	25				27	28	9	18	9	163

* Also with a visible primary focus

(Miller and Cashman 1955a) Calcification may spread to other glands in the line of lymphatic drainage.

When children undergo primary infection the site of infection can be demonstrated in at least four-fifths of cases if examination is sufficiently careful and observation long-continued (Miller 1956)

It is a matter of clinical experience that in children in this country the glands draining a hæmatogenous deposit, such as a joint or a metastatic abscess, rarely if ever become clinically enlarged or proceed to abscess formation.

If these facts are accepted, it follows that any group of tuberculous lymph-glands (wherever they arise) are likely to represent the gland component of a primary complex if they are the *sole* clinical or radiological sign of tuberculosis in the body

Results of Review

From the history and the results of clinical and radiological examination of the 163 children, we were able to group them as in the table

Occasionally in the original clinical records there was some difficulty in distinguishing between tonsillar and submandibular lymphadenitis, this applied to only a few cases, but we have taken these two sites together (at least 9 of every 10 were tonsillar) No child in this series had generalised tuberculous lymphadenitis, which must be extremely rare in English children We did see 2 children with bilateral cervical adenitis which became evident some years after primary pulmonary infection They form an uncommon but very interesting and puzzling type of cervical lymphadenitis and we refer to them later

We shall now consider the various topographical groups of glands, to determine how many were the only sign of tuberculosis (and therefore likely to be part of a primary complex), and to discover the evidence, if any, that the infection might be hæmatogenous ✓

Preauricular Glands (11 children) ✓

5 of these had primary foci on the skin of forehead or cheek, 3 on the palpebral conjunctiva of the upper eyelids, and 2 in the lacrimal sac. None had hæmatogenous lesions or calcification in any other group of glands We did not find a primary focus in the 11th child, and his tuberculous lesion was a small abscess on the cheek just above the angle of the jaw Though we cannot be sure we think that this was more likely to be a subcutaneous abscess than a preauricular adenitis (Miller and Cashman 1955b) Even at the follow-up examination we could not demonstrate the site of the primary complex

Other Glands Draining Face and Scalp (6 children) ✓

In each case a primary focus was found 1 in the scalp draining to occipital glands, 1 in the mouth to the supramandibular gland, 1 on the scalp to postauricular glands, and 3 on the chin to the submental glands The first child had miliary tuberculosis when he was first seen with the occipital adenitis, but he made a good recovery and did not have any other lymph-gland involvement. No other child had hæmatogenous lesions or calcification in any other group of glands

Axillary Glands (4 children) ✓

3 of these had primary lesions visible on the arm and tuberculous axillary adenitis without other manifestations of tuberculosis The 4th case was not so readily explained The child had a tuberculous abscess on the anterior wall of the axilla without any other signs of tuberculosis We think that, like the boy with the abscess on his cheek, she may have had a metastatic abscess, but again we have no evidence of the site of primary infection.

Epitrochlear Adenitis (2 children) ✓

We think both these children were inaccurately diagnosed 1 had a subcutaneous abscess on the inner aspect of the arm and a primary complex in the lung, the other had a lesion, described as an epitrochlear abscess, which was indeed a primary focus with an axillary adenitis and no other evidence of tuberculosis In both children the epitrochlear gland was intact.

Inguinal Adenitis (15 children) ✓

13 of these children had visible primary foci on the skin of foot, leg, or buttock The only child with bilateral inguinal adenitis had a primary lesion at the anus but crossing the midline to drain to both inguinal areas Not one of these 14 children had any other sign of tuberculosis The 15th child presented with an inguinal adenitis and a calcifying primary complex in the lung When she was first seen a small scabbed lesion was noted in the skin over the tendo achillis, but unfortunately was not further examined Two years later there was calcification in the inguinal gland and a small scar typical of a primary focus on the skin at the site of the original scab This girl almost certainly had a double primary infection—one complex in the skin and inguinal glands the other in the lung and mediastinal glands

Supraclavicular Adenitis * (7 children) ✓

Supraclavicular adenitis, unlike the adenitis in those groups just discussed, was not associated with visible primary foci But 4 children had mediastinal calcification and a 5th mediastinal and mesenteric calcification The association is clear but the mechanism is not so obvious, as well as draining to the

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* There is some difficulty about terminology The glands are those described in Gray's Anatomy [illegible] ed, pp [illegible], as subclavicular or inferior deep cervical, but clinically they present as masses just above the clavicle We have preferred to call the lesion 'supraclavicular adenitis'

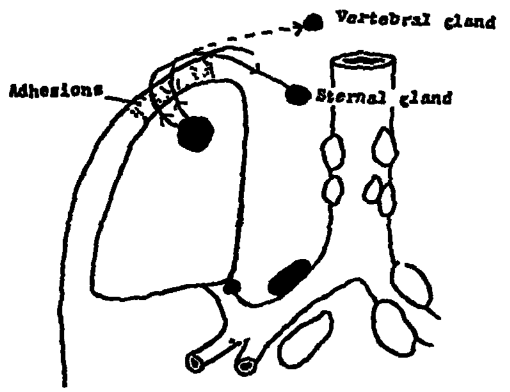

Fig 1—Drainage of apical primary focus to the sternal and vertebral glands in addition to the mediastinal glands (Scott and Beattie 1928)

mediastinal glands the infection from an apical primary focus might have spread through the apical pleura to the supraclavicular glands as described by Scott and Beattie (1928) (fig 1) A 6th child had a chain of calcification reaching down from the tonsillar gland, and the supraclavicular mass in this case was the lowest gland in the chain, yet for some reason it softened first The 7th child presents a difficult and as yet unexplained problem A strong healthy boy of 12 years presented with a large firm swelling above the medial end of the *right* clavicle (fig 2) The only other sign of tuberculosis was a small rounded lesion at the extreme apex of the *left* lung with slight hilar adenopathy The mass above the clavicle soon softened and was removed surgically, healing was quick Calcification can now be seen at the left apex and hilum of the lung, but *not* above the clavicle

It seems likely that he had a primary complex in the left upper lobe Direct spread to the *right* supraclavicular glands seems unlikely, and beyond suggesting that infection reached the left supraclavicular glands via the blood-stream, or that it did not arise in a lymph-gland, we cannot explain this case

Tonsillar and Submandibular Adenitis (118 children)

The tonsillar group of glands is by far the commonest site of peripheral tuberculous lymphadenitis Only 16 of these 118 children had bilateral lymphadenitis, and in only 9 of the 118 has calcification appeared without abscess formation In various ways we knew the time of infection in 33 of these children but we were able to see a *primary focus in the mouth* or tonsils in only 15 children The others were seen at very varying times after infection, for glands are often present for some years before an abscess forms and the child is sent to hospital

Fig 2—Swelling caused by tuberculous abscess in supraclavicular glands or in subcutaneous tissues Only other tuberculous lesion a primary complex at the apex of the left lung

9 of the 118 children had calcification in mediastinal glands, another 17 had calcification in mesenteric glands, and 1 had calcification in both mediastinal and mesenteric glands as well as cervical glands In all, therefore, 27 of the 118 children had evidence of central as well as peripheral calcification, leaving 91 in whom the cervical adenitis was the only sign of tuberculosis In this district in 1947, at least 85% of all primary infection in children was in the lung, but in these 118 children abdominal calcification was twice as common as pulmonary This distribution of calcification is almost certainly related to the manner of infection rather than to spread after infection

Although only 16 of the 118 children had bilateral tuberculous lymphadenitis, 8 of these 16 had calcification in other glands also—3 in the mediastinal, 4 in the mesenteric, and 1 in both In contrast only 19 of 102 children with unilateral calcification had other calcification This distribution again can hardly be accidental and a reasonable explanation is that when infection is heavy enough to give bilateral infection of cervical glands it is also more likely to give another simultaneous primary infection elsewhere

4 of these 118 children merit special mention

2 children with enlargement of cervical glands were found to have old abdominal calcification In one the cervical glands progressed to abscess formation and tubercle bacilli were recovered, in the other calcification appeared some two years later, and eventually these glands also softened The relationship of the tuberculous infection of these groups of glands is not clear because there seems no reason why mesenteric calcification should appear before cervical if the children had simultaneous oropharyngeal and abdominal primary infection. Yet we have already mentioned a very similar case of the girl who had a calcified complex in the lung and an inguinal adenitis which did not show calcification until two years later

The 2 others are even more puzzling They were both children who had been infected during infancy, and when first seen each had an old and well-calcified primary complex in the lung When 8 years old they both developed extensive tuberculous infection in the cervical glands The first child had a supraclavicular abscess on the right side and a large mass of tonsillar glands on the left, and the second had a chain of rubbery glands along both sternomastoid muscles, in the tonsillar, submandibular, and submental glands, and in both axillary glands No other glands were clinically enlarged and none apart from those mentioned above have calcified

These 2 children present such difficult problems that they need separate description, but they seem to represent a type of peripheral adenitis distinct from all others in this present series, and one which is uncommon in childhood

Discussion

The series comprised 163 children with superficial tuberculous swellings diagnosed originally as peripheral lymphadenitis After our review we think that in 4 of these children the superficial swellings were metastatic abscesses rather than lymph-gland abscesses In 127 (80%) of the remaining 159, the peripheral lymphadenitis was the only evidence of tuberculosis found over a long period of observation We think that in those children it represented the gland component of a primary complex and reflected the site of the primary infection The primary focus was seen in only 48 of the children and is much more likely to be seen in children with inguinal, axillary, or preauricular adenitis than in those with tonsillar adenitis

The remaining 32 (20%) children had calcification in " central " glands as well as peripheral tuberculous lymphadenitis In 28 of these the central calcification was associated with tonsillar adenitis In this group there was at least the possibility that the peripheral adenitis was the result of hæmatogenous spread from the central glands But there are several pieces of indirect evidence which together suggest that this is unlikely

12 of the 159 children had undoubted hæmatogenous lesions, but none of these had central as well as peripheral calcification

If the peripheral adenitis had followed hæmatogenous spread, the distribution of the central primary complexes should have been the same as in the general population We have already seen that in our group mesenteric calcification was twice as common as mediastinal, whereas in the general population at that time lung primary infection was at least five times as common as abdominal infection. This very unusual distribution in our group suggests a relationship with the mechanism of infection rather than events after infection

In several of the 32 with both central and peripheral calcification there was more direct evidence that the peripheral lymphadenitis was not the result of hæmatogenous spread Thus 2 children had a visible primary focus on the skin in relation to the peripheral adenitis, in another 5 seen during the initial fever of primary infection the peripheral lymphadenitis appeared as the child became tuberculin-positive

We therefore think that multiple simultaneous primary infections must occur, and we suggest that the ingestion of infection is the explanation of the association of cervical and mesenteric calcification. We know, too, that children in contact with infective adults occasionally get a primary infection in the oropharynx and a simultaneous pulmonary primary complex by inhalation

Hence simultaneous primary infection seems to be at least as good an explanation as hæmatogenous spread in most of these 32 children with peripheral and central calcification From this statement we must, however, exclude certain of our cases of special interest, and in particular the 2 children whose cervical lymphadenitis did not arise until some years after this primary infection in the lung

From this analysis we conclude that, in English children for the period under review, at least 80% (and probably well over 90%) of all peripheral tuberculous lymphadenitis represents the gland component or the direct lymphatic drainage of a primary complex

Summary

We have presented the results of a review of 163 children with superficial swellings diagnosed as tuberculous lymphadenitis 4 of these swellings appeared to be superficial tuberculous abscesses rather than lymph-gland infections In 127 (80%) of the remaining 159, the peripheral adenitis was the only sign of tuberculosis In 32 (20%) there was calcification in mediastinal or mesenteric glands as well as peripheral tuberculous lymphadenitis, we give reasons for attributing most of these to simultaneous primary infection rather than hæmatogenous spread from central to peripheral glands. We draw attention to 2 children with an unusual form of extensive tuberculous lymphadenitis arising years after a primary infection in the lung

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"It is no part of the job of a scientist to tell people that they must stop breeding because it would be inconvenient to have to feed more than a certain number The scientist's job is to fool around less with sputniks and the moon's backside and settle down to produce the food that is needed At the same time he should try to give people the means of having the number of children they positively want Most of us are probably now conceived inadvertently, so that this measure of control would have the effect of diminishing pressure on food supplies But the motive behind the research should be the duty to try to give people what they consciously want rather than the arrogant wish to tell them what they ought to want"—N W PIRIE, *New Statesman*, Jan 25, 1958, p 100

ALKALINE PHOSPHATASE IN THE WHITE CELLS IN LEUKÆMIA AND LEUKÆMOID REACTIONS

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IN 1946 Wachstein, by a cytochemical technique, demonstrated that alkaline-phosphatase activity in the blood-cells is almost confined to the mature segmented neutrophils Normal polymorphs contain only small amounts of this enzyme, but in acute infections and after hæmorrhage, trauma, or infarction the quantity increases considerably In chronic myeloid leukæmia, on the other hand, there is little or none of this enzyme in the white cells, whatever the stage of the disease

Valentine and Beck (1951), Valentine et al (1952), and Wiltshaw and Maloney (1955) confirmed Wachstein's findings The method used by Valentine and colleagues is more strictly quantitative than that of Wachstein phosphatase activity is determined on a plasma-free suspension of white cells and expressed in milligrammes of phosphorus liberated per hour at 37°C by 10^{10} white cells at pH 9·9 They found the mean level to be 25·8 units in health, 119·1 units in acute infections, 4·0 units in chronic myeloid leukæmia, and 82·0 units in polycythæmia vera

Our purpose here is to illustrate the value of a simple cytochemical technique in distinguishing between (1) myeloid leukæmia and (2) leukæmoid reactions involving the myeloid series of cells Such reactions are seen in a variety of diseases—e g, Hodgkin's disease, tuberculosis, carcinomatosis, polycythæmia vera, myelosclerosis, and hæmolytic anæmias

Investigation

Method

The cytochemical technique we have used is a modification of Gomori's original method for demonstrating alkaline phosphatase

(1) Fix the blood or marrow smears for thirty seconds in a mixture of 10 ml of formalin to 90 ml of absolute methyl alcohol

(2) Wash for a few seconds and then incubate for two hours at 37°C in a freshly prepared buffer substrate solution containing 30 ml of 10% sodium barbitone, 30 ml of 3·2% sodium β-glycerophosphate, 30 ml of M/10 magnesium sulphate, 45 ml of 2% calcium nitrate, and 165 ml of distilled water

(3) Rinse the slides for a few seconds in distilled water containing a few drops of 2% calcium-nitrate solution

(4) Immerse the slides in 2% cobalt-nitrate solution for five minutes

(5) Wash well and treat for ten seconds in a weak solution of ammonium sulphide (about 1 ml of ammonium sulphide to 80 ml of water)

(6) Wash well and counterstain with 2% aqueous solution of G T Gurr's safranine O for ten seconds

(7) Wash well and mount.

Control blood films of known high leucocyte-phosphatase activity and of normal blood are put through at the same time Stock solutions of 3·2% sodium β-glycerophosphate, 10% sodium barbitone, and the formalin-methyl alcohol fixative are kept at 0–4°C until they are required.

Interpretation

Alkaline-phosphatase activity is shown as black granules in the cytoplasm of the neutrophil polymorphs lymphocytes, monocytes, plasma cells, eosinophils, and all blast cells show

Disease (no of observations)	Percentage of cells with phosphatase activity					
	Strong activity		Weak activity		No activity	
	Range	Mean	Range	Mean	Range	Mean
Normals (50)	0–2	1 0	14–82	18	25–90	82 0
Chronic myeloid leukæmia (50)	0–1	1 0	0–24	6	75–100	92 0
Polycythæmia vera (50)	30–95	65 0	5–65	32	0–6	3 0
Leukæmoid reactions (17)	25–92	60 0	10–70	34	0–14	6 0

no activity, but they can be distinguished by their affinity for safranine Phosphatase activity is expressed as absent, weak, or strong (see figs 2 and 4), and an assessment is made by examining 400 consecutive neutrophil polymorphs

Results

The range and mean percentages of cells showing strong, weak, or no activity in healthy people and in patients with chronic myeloid leukæmia, polycythæmia vera, and leukæmoid reactions are shown in the table Normal polymorphs show no activity, or weak activity represented by a few small black granules in the cytoplasm Strongly positive cells show many coarse black granules, or the whole cytoplasm appears densely black Such cells are rarely seen in normal blood and were never more than 2% of the total count

In all 50 cases of *chronic myeloid leukæmia* phosphatase activity was much reduced or absent Strongly positive cells were not seen This was true at all stages of the disease, irrespective of treatment and of the white-cell count

In *polycythæmia vera* strongly positive cells were often predominant, especially when the white-cell counts were raised

17 cases of *leukæmoid reactions* involving the myeloid series were investigated, invariably they showed a high proportion of strongly positive cells The leukæmoid reactions were associated with the following diseases Hodgkin's disease (6), myelosclerosis (3), carcinomatosis (2), tuberculosis (2), acquired hæmolytic anæmias (2), and reticulosarcoma (2) In all, the cytology of the blood and the marrow, when examined by ordinary staining techniques, was identical with myeloid leukæmia, and initially leukæmia was often diagnosed

The following examples illustrate these points

Case 1—A Regular Army corporal, aged 21, had much enlarged cervical lymph-nodes Blood examination red cells 3,900,000 per c mm, hæmoglobin 11 9 g per 100 ml, platelets 125,000 per c mm, white cells 44,000 per c mm (polymorphs 91 5%, lymphocytes 2 0%, monocytes 4 5%, eosinophils 1 0%, myelocytes 0 5%, blast cells 0 5%) The marrow picture (fig 1) was indistinguishable from myeloid leukæmia, the predominant cell being the myelocyte

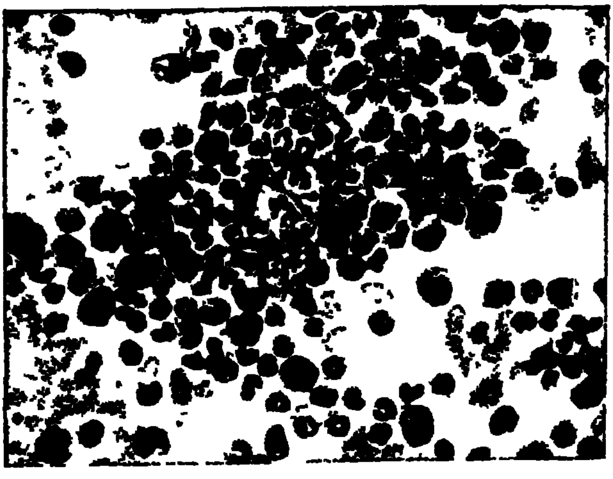

Fig 1—Case 1 (Hodgkin's disease) sternal marrow showing considerable hyperplasia of myeloid series of cells (Jenner-Giemsa)

Phosphatase test (fig 2) strongly positive 78%, weakly positive 18%, no activity 4% The high percentage of strongly positive cells was very much against the diagnosis of myeloid leukæmia Because of this a cervical lymph-node was excised, which showed typical Hodgkin's disease The patient is alive and well three years after these investigations were made

Case 2—A man of 26 had considerably enlarged cervical lymph-nodes Blood examination red cells 3,100,000 per c mm, hæmoglobin 10 1 g per 100 ml, platelets 105,000 per c mm, white cells 26,000 per c mm (polymorphs 92%, lymphocytes 6%, myelocytes 2%) The marrow smears (fig 3) were exactly like those in case 1—i e, indistinguishable from myeloid leukæmia

Phosphatase test (fig 4) strongly positive cells 0, weak 6%, no activity 94% A cervical lymph-node showed typical leukæmic infiltration The patient died two months later At necropsy there was leukæmic infiltration of his liver, spleen, skin, lymph-nodes, and marrow

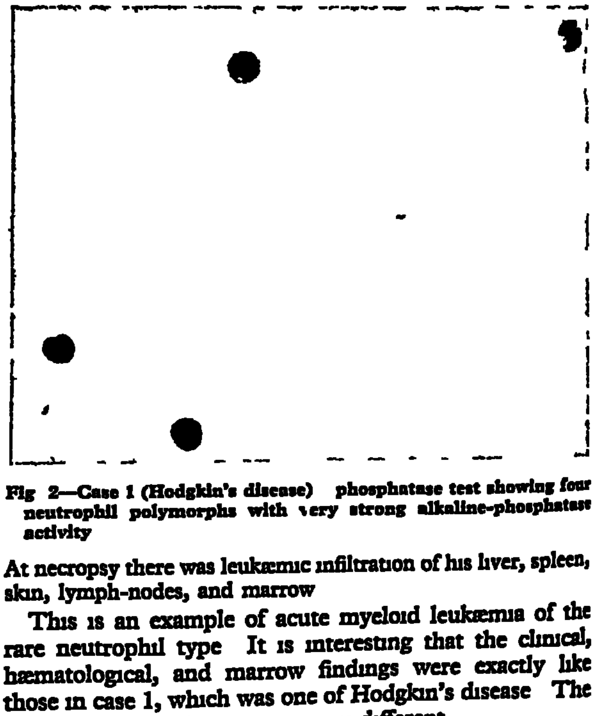

Fig 2—Case 1 (Hodgkin's disease) phosphatase test showing four neutrophil polymorphs with very strong alkaline-phosphatase activity

This is an example of acute myeloid leukæmia of the rare neutrophil type It is interesting that the clinical, hæmatological, and marrow findings were exactly like those in case 1, which was one of Hodgkin's disease The prognosis in the 2 cases was very different

The phosphatase test is usually of no value in the acute leukæmias, because blast cells contain no phosphatase However, in acute myeloid leukæmia of the neutrophil type (case 2 is an example of 2 such cases studied), where there is enough differentiation of the white cells to make the test feasible, the results are the same as for chronic myeloid leukæmia—a gross decrease of leucocyte alkaline phosphatase

Case 3—A man, aged 61, with polycythæmia vera was satisfactorily controlled for eleven years by exposures to whole-body irradiation and occasional venesection He then developed progressive enlargement of the spleen, the hæmoglobin and red cells fell slightly, and there was a considerable rise in the white-cell count, which previously had been within normal limits Blood examination red cells 5,320,000 per c mm, hæmoglobin 15 1 g per 100 ml, white cells 71,000 per c mm (polymorphs 70%, lymphocytes 5%, monocytes 5%, eosinophils 1 0%, basophils 6 0%, promyelocytes 2 5%, myelocytes 10 5%), nucleated red cells 41 per 200 white cells The blood and marrow smears were compatible with chronic myeloid leukæmia

Phosphatase test strongly positive 92%, weakly positive 6%, no activity 2% Biopsy of an iliac crest showed myelofibrosis

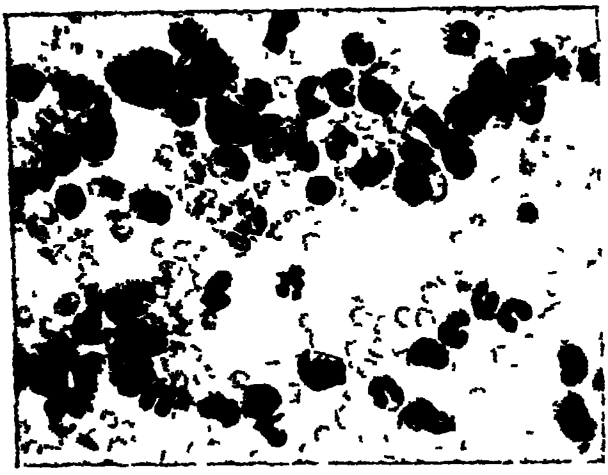

Fig 3—Case 2 (acute neutrophil leukæmia) sternal marrow showing considerable hyperplasia of myeloid series of cells. (Jenner-Giemsa.)

A splenogram confirmed a considerable extramedullary hæmopoiesis, 45% of the total nucleated cells being normoblasts of the intermediate and late types, including many in mitosis

This is an example of polycythæmia vera pursuing a long clinical course and ending in myelofibrosis, the splenic enlargement was due to extramedullary hæmopoiesis, and the white-cell changes were leukæmoid and not leukæmic. This distinction is important because radiotherapy and chemotherapy are contraindicated in the presence of myelofibrosis

Discussion

The cytochemical method of demonstrating leucocyte alkaline phosphatase, as described above, is easily applied and is often the only means of distinguishing between myeloid leukæmia and leukæmoid reactions involving the myeloid series of cells The modifications used include a different fixative, a much shorter incubation period, and a different counterstain Kaplow (1955) found that the mixture of formalin and methyl alcohol gave better cytological details than other tried fixatives

The absence or considerable reduction of leucocyte alkaline phosphatase consistently found in chronic myeloid leukæmia appears to precede any other definite cytological abnormality in the evolution of this type of leukæmia Thus, Maloney and Lange (1954) described the preclinical stage of 4 cases of myelogenous leukæmia developing in atomic-bomb survivors and found that very low alkaline-phosphatase levels in the leucocytes preceded any definite cytological evidence of leukæmia in the blood or the marrow

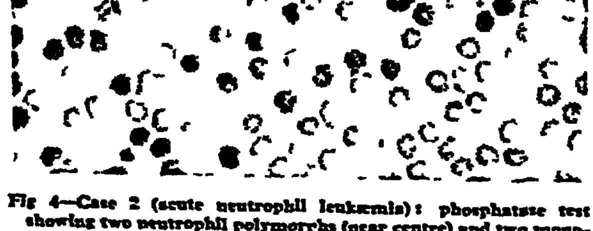

Fig 4—Case 2 (acute neutrophil leukæmia): phosphatase test showing two neutrophil polymorphs (near centre) and two mononuclear leucocytes (to left) without any alkaline phosphatase.

The leukæmoid reactions we have investigated were due to a great variety of diseases, including Hodgkin's disease, reticulosarcoma, carcinomatosis, hæmolytic anæmia, myelofibrosis, and tuberculosis They could not be differentiated from leukæmia by examining ordinarily stained blood and marrow smears, but in all of them the white-cell alkaline phosphatase was considerably increased. In the past many of these would have been classified as neutrophil leukæmias However, in 2 examples of neutrophil leukæmia which we have investigated, phosphatase studies showed a gross reduction in leucocyte-phosphatase activity It is evident that morphologically identical blood-pictures may be due to entirely different diseases and that leucocyte-phosphatase determinations are of assistance in distinguishing between myeloid leukæmia and leukæmoid reactions involving the myeloid series To establish the cause of the leukæmoid reaction it is necessary to use all the available clinical data and further assistance from histological studies—e g, by biopsy of lymph-nodes, iliac crest, spleen, &c

The precise role of alkaline phosphatase in the white cells is unknown Valentine (1956) and Valentine et al (1957) think that, in stress conditions—e g, after infection, hæmorrhage, intoxication, infarction, and trauma—there is a considerable rise in the activity of this enzyme in the white cells These stress phenomena have as their common denominator an increased pituitary-adrenal activity In normal people both cortisone and corticotrophin increase the activity of alkaline phosphatase in the leucocytes, but, when adrenal function is reduced (as in Addison's disease), though 17-hydroxycorticosteroids produce a similar increase, corticotrophin does not Valentine has also shown that, in uncomplicated rheumatic fever, rheumatoid arthritis, and some collagen disorders, there is not the expected increase in alkaline phosphatase in the leucocytes

Phosphatase was determined in 2 cases of acute leukæmia treated with cortisone in which there was complete clinical and hæmatological remission In spite of the apparent complete normality of the blood-cells, the neutrophils possessed considerably increased alkaline-phosphatase activity, which persisted until the leukæmia relapsed

Case 4—A woman of 36 was found to have acute lymphatic leukæmia Blood examination red cells 1,510,000 per c.mm, hæmoglobin 4 4 g per 100 ml, platelets 10,000 per c.mm, white cells 8200 per c.mm (polymorphs 2%, lymphocytes 34%, lymphoblasts 64%) Her marrow was considerably hyperplastic, the predominant cell being the lymphoblast. The phosphatase test did not show any activity in the white cells

After treatment with cortisone 200 mg daily for thirty-eight days there was a complete remission Blood examination red cells 4,320,000 per c.mm, hæmoglobin 14 4 g per 100 ml, platelets 265,000 per c mm, white cells 6000 per c.mm (polymorphs 68%, lymphocytes 30%, monocytes 2%)

Phosphatase test strongly positive 82%, weakly positive 12%, no activity 4% Treatment with cortisone 100 mg daily was continued and 68–94% of the neutrophils had strong phosphatase activity until the patient relapsed and died of leukæmia about three months later

Occasionally in acute leukæmias of all types an intercurrent infection causes a few strongly positive neutrophils to appear in the peripheral blood, but this was exceptional, and they never constituted more than 10% of the total count

In 2 cases of polycythæmia vera, after satisfactory control of the total red-cell mass with intramuscular injections of triethylenethiophosphoramide there was a marked reduction in the leucocyte phosphatase which lasted until the red cells started to increase in number again

With these exceptions the results have been consistent We believe that the finding of a high alkaline-phosphatase level in the leucocytes indicates the need for further clinical and pathological studies before a diagnosis of leukæmia can be made with confidence

Summary

A simple cytochemical technique for demonstrating alkaline-phosphatase activity in leucocytes is described

In chronic myeloid leukæmia and acute neutrophil leukæmia this activity is reduced or absent

In leukæmoid reactions due to Hodgkin's disease, myelofibrosis, reticulosarcoma, carcinomatosis, polycythæmia vera, hæmolytic anæmia, and tuberculosis very high levels of alkaline phosphatase were found in the leucocytes

The amount of alkaline phosphatase in the leucocytes appears to be regulated by the pituitary-adrenal axis In complete remission in 2 cases of acute lymphatic leukæmia following cortisone therapy, in spite of the apparent normality of the white cells, the phosphatase levels were high and remained so until the leukæmia relapsed

The determination of alkaline phosphatase in the leucocytes is at present the best, and often the only, means of distinguishing between myeloid leukæmia and leukæmoid reactions involving the myeloid series of cells

We wish to thank Prof A C P Campbell for his helpful criticism and for reading the manuscript Mr N Mowat, F I.M L T, kindly took the photomicrographs

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ARTERIAL REPLACEMENT WITH MINIMAL INTERRUPTION OF BLOOD-FLOW

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SURGICAL excision of a portion of artery involves temporarily shutting off the circulation through that artery Insertion of a graft may take many minutes, and in the case of a carotid artery even a short period of occlusion is fraught with danger Even with hypothermia the time-limit of tolerance may be scarcely adequate for the task in hand, and the alternative of a temporary shunt circulation has its own difficulties

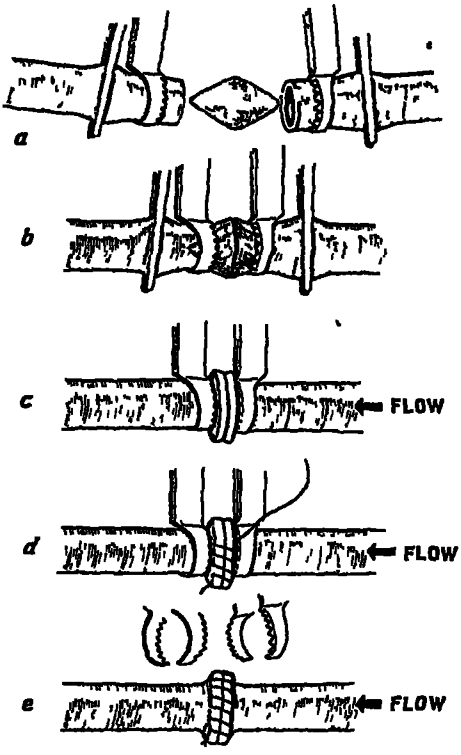

Fig 1—The ice-cone method For description see text

The problem is to join two cut ends of artery with such speed and certainty that restoration of the circulation within a few seconds can be guaranteed We felt that the solution would be found in a method permitting immediate accurate approximation of the two artery ends so that flow can take place while the ends are being sutured, and we believe that we have found such a method

The Ice-cone Method

Each of the two artery ends is placed in a toothed ring with a small portion protruding, a double cone of ice is inserted into the adjacent open ends (fig 1a), and the rings are now brought together The teeth of the rings so engage the artery wall that the cut ends must turn either outwards or inwards They cannot turn inwards, because the ice fully occupies the available space, and they are therefore obliged to flange outwards (fig 1b) When the rings are fully closed, there is between them an outward-turned flange of each artery, and the two trumpets so formed by the arteries are held firmly together by the toothed rings so that the lumen of one continues without interruption into the lumen of the other (fig 1c) Flow will start again as soon as the ice melts, at body-temperature this happens in a few seconds With the circulation restored, the flanged ends of the arteries can be sutured at leisure (fig 1d) When the suture line is completed the ring clamps are reopened and removed, this is possible because in fact each ring is constructed of two half rings which separate to allow disengagement from the artery There now remains a conventional type of anastomosis (fig 1e)

For this simple procedure to work with speed and certainty, the following conditions must be fulfilled

The rings must be slightly less in diameter than the unstretched artery—otherwise the artery cannot expand beyond the ring to form a flange, and may slip through the ring Likewise, the ice shape must have a maximum diameter slightly greater than the rings If the ring is of much smaller diameter than the artery anastomosis is still possible, but the advantages of the method are lost, because when the artery is compressed its walls are thrown into longitudinal folds, this obstructs the lumen, preventing the early flow which is the primary object of the method

The teeth must be sharp and long Small ineffective serrations cannot secure sufficient grip on the artery except by crushing it

The rings must be opposed with enough force to press the arteries against the yielding ice, so that at no time can either artery slip inside the other, but the force must not be too great or the intima will be severely nipped against the ice and fractured

To make the double cone of ice, a latex-rubber mould, of the correct size and shape, is filled with heparinised saline and placed in a container surrounded by carbon-dioxide snow, the ice cone is ready for use within an hour, and is left undisturbed until needed This process is not difficult, and when brought from the container and squeezed from its rubber mould the ice remains solid long enough for it to be used without haste All the materials to be used are sterilised at the outset

While the artery ends are brought over the ice cone, the vessels must be held and occluded by artery clamps Initially we made an instrument with ring clamps separate from the artery clamps, but this proved awkward to use because the operator was aligning three independent movable components —two artery clamps and the ring clamp , moreover, it was difficult to compete with any tension These difficulties were overcome by redesigning the instrument so that the ring-anastomosis clamp can be temporarily attached to a hinged twin set of arterial clamps

The complete apparatus consists therefore of two instruments—a ring-anastomosis clamp (stippled in fig 2a) and a twin set of artery occlusion clamps—which fit together, each assisting the action of the other

Fig 2a shows the double instrument with clamp and half rings of the left half closed as if encircling an artery, the clamp and spring-mounted half rings of the right half are open ready to place over an artery When either clamp is closed, its small side arms bring the corresponding spring-mounted half rings together to form a complete ring, thus at one movement circulation is arrested, and the artery is firmly held by the instrument and encircled by the ring

When the main locking-ratchet is released, the circular spring of the ring-anastomosis clamp brings the two halves of the double instrument together, approximating the two anastomosis rings As these rings come together, self-locking arms secure the half rings so that they will not open when the artery clamps are removed After removal of the clamps there is left in situ a comparatively small instrument, which may be rotated even within a small operation field to facilitate the suturing of the double flange of artery

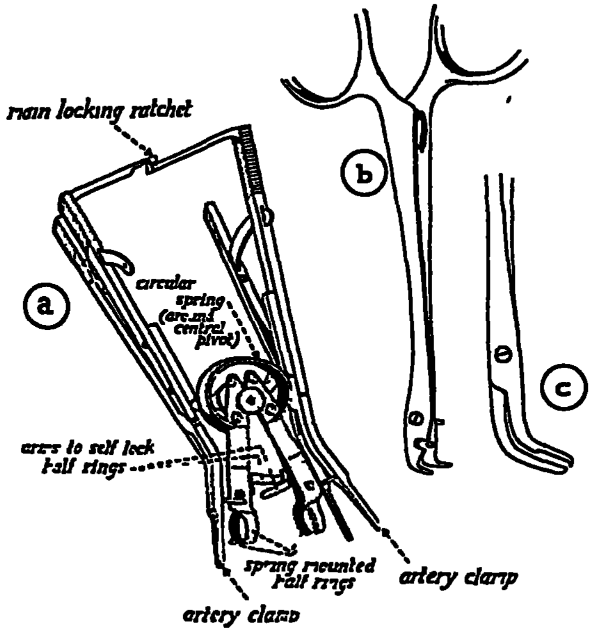
main locking ratchet
b
a
circular spring (around central pivot)
c
arms to self lock half rings
spring mounted half rings
artery clamp
artery clamp

Fig 2—(a) Combined ring-anastomosis clamp and artery-clamps for the ice-cone method (see text) (b) Separator for opening the ring-anastomosis clamps. (c) Handling tool for gripping ring-anastomosis clamp during suture of the artery

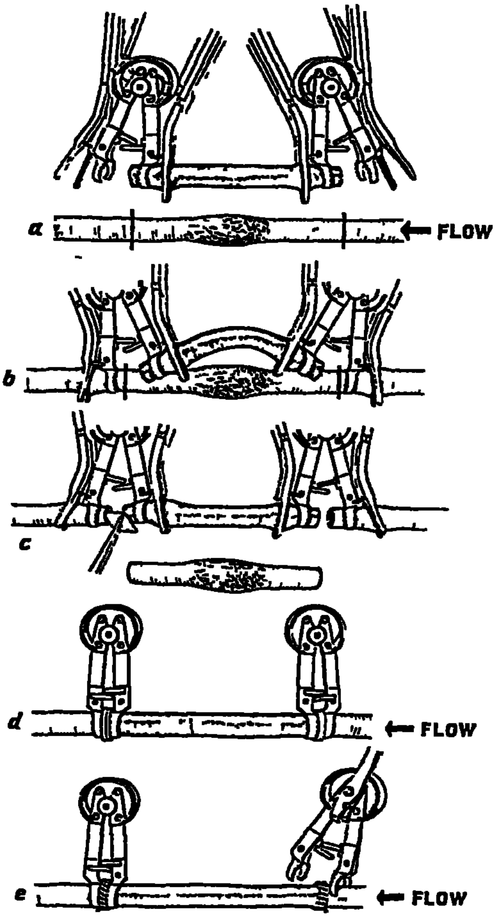

Fig 3—The replacement of a segment of diseased artery by a graft artery using the ice-cone method The time-interval between a and d is about 60 seconds

Fig 3 shows how the instrument may be put to practical use for the replacement of a portion of artery by a homograft Fig 3a shows a graft of suitable length, with a ring-clamp device attached to each end, laid alongside the diseased artery The outer half of each anastomosis device is now placed in position on the host artery, above and below the defect Simultaneous closure of both artery-clamps shuts off the circulation, locks the devices to the artery, and encircles the artery with the rings (fig 3b) The diseased segment is freed by division of the artery about 1 cm inside the outermost anastomosis rings Each device now holds a cut end of host artery and an end of the replacement graft in position ready for anastomosis (fig 3c) Immediately after insertion of the ice cones and closure of the two anastomosis clamps the artery clamps are released, so that flow may restart as soon as the ice melts The artery-clamps are disengaged and removed, leaving the two ring clamps in position (fig 3d) Suturing is completed while flow continues, and finally the ring clamps are opened and removed completely (fig 3e)

Experimental Results

This method has been tried both on human cadavers and on living animals Only common carotid or arteries of similar calibre have been used so far

Identical arteries—The instrument worked unerringly in the anastomosis of healthy vessels of similar calibre

Arteries from different subjects—The instrument had considerable latitude with regard to differences in calibre and texture of the arteries being anastomosed It never failed to anastomose two healthy arteries of the same anatomical name or of even approximately similar size Of fifty specimens, five common carotid arteries were found to be too small for the ring size designed for this vessel but were readily anastomosed by use of a slightly smaller ring

Atheromatous arteries.—Slight atheromatous thickening made little difference, though an inelastic thickened artery might tend to force a supple opposing artery to form a cuff on itself This did not, however, prevent the method from working The more severely atheromatous artery on occasions proved too unyielding for the instrument, and undue force tended to split the artery This could be remedied by making three slits in the inelastic intimal layer, so that the artery flanged readily as the three slits opened out Thorough removal of obliterating material in the partially or completely occluded artery left a supple vessel, well suited for the method We conclude that the device will handle without difficulty a properly disobliterated artery

Plastic arterial protheses—Orlon-cloth and polyvinyl-sponge tubes were well accepted

Relatively inaccessible arteries, such as the internal iliacs, were anastomosed more easily with the device than with conventional methods

Veins—The method has not yet been extensively applied to veins Limited experiments indicate that it is fully applicable though the serrations on the ring clamp may have to be modified

Experiments were done on the canine thoracic aorta because in size it matches the human carotid artery and because any undue delay in opening the circulation will be evident by renal failure or by spinal-cord damage In four dogs, 3 in lengths of homografts or heterografts were inserted into the descending thoracic aorta, this was accomplished with occlusion of flow for less than 7 minutes in each case The early version of the device was used for these experiments These animals recovered without difficulty and remain well after several months

In two dogs the latest version of clamp (fig 3) was used to insert 2 in lengths of grafts into the descending thoracic aorta This improved version proved successful, and circulation was restored within 4 minutes of the first occlusion Unfortunately a defect in the respirator caused the death of one dog while the chest was being closed The other dog remains well after several months In a third, an unusually large thoracic aorta was successfully "grafted" by use of suitably large ring clamps, this took 6 minutes, since each end of the replacement graft was anastomosed separately (not simultaneously) because of poor access through a small incision This animal remains well

Case-report

As these experiments were encouraging, we decided to try the method clinically

The patient selected suffered from severe claudication in both calves, due to bilateral block in the superficial femoral arteries At operation a homograft was inserted between the commencements of the superficial femoral arteries and the mid popliteal arteries, thrombendarterectomy was necessary for the upper part of each superficial femoral artery As the available grafts were not long enough, two homografts were anastomosed together for each side All the various anastomoses were end-to-end, and with the exception of the right upper anastomosis all were performed by the ice-cone method The circulation on each side was reopened within a few minutes and maintained through the ring clamps while suturing was completed On removal of the ring clamps there was negligible leakage through the suture lines and all anastomoses appeared to be of high standard An excellent pulsatile blood-flow to both feet has persisted over the two months since this operation

The method thus proved satisfactory on the moderately thickened arteries commonly encountered in this class of patient, and it avoided stagnation of the circulation from prolonged occlusion of the main femoral artery

Though the use of a soluble obturator in arterial anastomosis is not a new conception, our ice cone has, we believe, considerable advantages over the dextrose rod recommended by Smith (1945)

Summary and Conclusions

A method of arterial anastomosis, designed to allow nearly immediate restoration of blood-flow, is described It depends on the use of an ice shape and ring anastomosis clamps, it has proved very successful in dogs and has also given satisfaction in the one case of arterial *replacement* in man in which it has been tried By this method a portion of artery may be replaced by a graft with only brief interruption of the blood-flow

Though the method has not yet been tried sufficiently for us to recommend its use, except tentatively, in man, it appears promising It may offer a practicable means of anastomosing small vessels as well as large ones

The instrument is made by Messrs Thackray, 10, Park Street, Leeds, who will supply it for experimental purposes, but we wish to emphasise that the method can not yet be generally recommended for use in man The instrument incorporates important suggestions by Mr A B Hallam, of Messrs Thackray, who personally made the prototypes We wish to thank him and Messrs Thackray for their most valuable assistance in its development

We are indebted to Mr D P Hammersley for the illustrations

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PLASTIC BAGS FOR STORING AND TRANSFUSING BLOOD

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PLASTIC bags for storing and transfusing blood were first introduced at Harvard Medical School in the late 1940s to facilitate research projects in the fractionation of blood The technique has since been developed commercially (Walter and Murphy 1952), largely as a result of the stimulus of the Korean campaign, and plastic equipment is now extensively used in the United States of America The present investigation was undertaken to test the suitability of one type of this equipment under conditions in this country and to ascertain if the published reports on the superiority over glass equipment could be substantiated

Source of Materials and Methods

The plastic bags were the 'Fenwal' type manufactured by the firm of that name at Framingham, Mass, U S A Fenwal bags are of the so-called type-1 design—i e, the tube that leads from the donor is an integral part of the bag and remains attached to it once withdrawal of the blood has been completed In the Fenwal system this donor tube may be used as a source of blood for cross-matching—i e, it forms an "integral" pilot tube Transfusions of blood from plastic bags were made with Fenwal giving sets, which resemble closely in basic design the experimental set tested by the Medical Research Council (1957)

A study was made of the general suitability of the plastic equipment as regards handling, filling, storing, mixing, and delivering

In six healthy young adult males the survival of the individual's own erythrocytes on reinjection into his own circulation was compared after storage in glass and in plastic

In three of the subjects blood was stored first in plastic and then in glass and the order was reversed in the other three

The same anticoagulant, in the same proportion relative to the blood withdrawn, was used in the plastic and in the glass containers This anticoagulant was prepared according to formula A of the U S P (dextrose 2 45 g , citric acid 0 8 g , trisodium citrate 2 2 g , water to 100 ml) 75 ml of this solution is contained in the plastic bag, and 60 ml was transferred directly from a bag to the glass bottles used for the trial In each case blood was stored for 28 days at the same constant temperature

The survival of red cells was measured with ^{51}Cr (Mollison 1956) The radioactivity in samples of blood was measured in a scintillation counter (Ekco Type N550) To estimate loss of labelled red cells from the subject's circulation between the time of injection and withdrawal of the first (10-min) sample of blood, the volume of red cells was estimated indirectly by the Evans-blue (T1824) technique of Crooke and Morris (1942) and from the dilution of ^{51}Cr-tagged cells in the circulation, the 10-min sample being used The red-cell volume measured by the dye technique was accepted as the " true " figure and used in each case to calculate the 100% value for the ^{51}Cr-tagged cells

TABLE I—WEIGHTS AND VOLUMES OF PLASTIC AND OF GLASS EQUIPMENT

Apparatus	Weight (g)
1 plastic bag with anticoagulant	113
4 plastic bags—airtight can	580
1 M R.C. bottle-waisted pattern with anticoagulant	590
	Volume (c.cm)
16 empty bags in airtight can	4014
4 glass bottles	6227
4 full bags (approximately)	3572

Hæmatocrits were corrected for trapped plasma and body venous hæmatocrit ratio (Chaplin and Mollison 1952, Mollison 1956)

Results

General suitability —The equipment was no more difficult to handle than conventional systems Weight-saving of a plastic bag over a bottle was very considerable, and volume-saving on full bags was slightly less than 50% (table I)

Filling—Ordinary gravity-filling was used The bags are designed to hold 500 ml of whole blood—more than is usually withdrawn in this country Unless some means of weighing the bag is used (equipment for this is, of course, available), it is difficult to tell when the flow should be stopped The time taken to collect 500 ml of blood varied from 6½ to 8 minutes, which compares favourably with the time required to fill a conventional glass bottle

Mixing —Blood stored in plastic bags proved as difficult to mix as that preserved in glass bottles Table II gives the packed-cell volumes of representative samples of blood drawn from plastic and glass containers after the gentle agitation usually undertaken before administration Blood from these containers, when fully mixed, had a packed-cell volume of about 40%

Delivery-rates —Table III summarises the results of delivery trials under different conditions The size of the tubing of the giving sets is of more importance than the container in determining the rate of flow of blood under gravity The performance of a plastic bag for pressure transfusion by hand is unsatisfactory compared with the standard equipment in use in this country, but again the difference is largely a result of the dimensions of the giving set Squeezing a plastic bag is effective but tiring, and this experience is in accord with that of J M Howard in Korea (personal communication)

TABLE II—PACKED-CELL VOLUME OF STORED BLOOD AFTER MIXING BY GENTLE AGITATION

Subject no	Method of storage	
	Plastic	Glass
1	33·0	27·0
2	27·0	49·5
3		13·0
4	15·5	74·0
5	29·0	
6	29·0	45·0

TABLE III—RATES OF FLOW

—	Flow (ml per min)
Free gravity flow (135 cm head, means of 4 experiments)	
Plastic bag—plastic giving set (residual blood in bag =30 ml)	56
Same—with prefiltered blood (no residual)	66
Standard bottle—giving set—standard glass-rubber set (filter in bottle)	81
Standard bottle—plastic giving set	69
Pressure infusions	
2-handed pressure on plastic bag	155
Standard bottle and glass-rubber set—sphygmomanometer bulb	394
Standard bottle—plastic giving set and sphygmomanometer bulb	116

All experiments used the National Blood Transfusion needle

Multiple transfusions out of plastic bags through the same giving set did not prove satisfactory In one such case less than half the rate achieved with the first bag under conditions of force flow proved possible with the second

Red-cell survival —Table IV lists the 24-hour figures for red-cell survival 24 hours after transfusion When a sample was not drawn at exactly 24 hours, this figure was derived from the survival curve The survival of erythrocytes after storage showed considerable variation from one individual to another, as had previously been reported by Mollison (1956) for glass containers Nevertheless there was a close similarity between the survival of erythrocytes in the same individual when reinjected into his own circulation, whether they were stored in plastic or in glass, and it was clear that improvement in red-cell survival is not brought about by storage in plastic containers under the conditions of this test

Discussion

The advantages claimed for plastic bags are less weight and a smaller volume for storage, freedom from air embolus in pressure transfusion, integral pilot tube, disposability, and better preservation of blood

TABLE IV—PERCENTAGE SURVIVAL 24 HOURS AFTER TRANSFUSION OF RED CELLS STORED BY DIFFERENT METHODS

Subject no	Method of storage	
	Plastic	Glass
1	64·0	62·0
2	57·0	60·0
3	81·5	87·0
4	84·0	87·0
5	57·0	61·0
6	66·0	78·0

Weight advantages for both empty and full bags are obvious, but it should be noted that the saving of space is nothing like so great as that of weight Pressure transfusion is certainly free from air embolus but, unless special equipment for compressing the bag is available, it is slower than the conventional bottle methods The integral pilot tube could be a real advantage, particularly to those who object to opening bottles for matching blood (Campbell 1956) Except under the conditions of war, the advantages of disposability will rest on cost, and at present the cost of plastic transfusion equipment is probably nearly twice that of conventional apparatus

It has been suggested that the overall design of the set (laminar flow hæmorepellent surfaces, and the absence of glass) favours the preservation of all the elements of the blood and in particular prolongs the storage life of the red cells The clinical evidence for the first statement is scanty, and that for the second is based on three experiments by Strumia (1955) and by Strumia et al (1955), in which blood stored for 21 days showed better survival if stored in plastic than if stored in glass These results were obtained from two autotransfusions and one transfusion with a compatible recipient and do not give a satisfactory estimate of the difference between plastic bags and glass bottles Gibson's (1956) figure of 10% superiority of survival of red cells stored in plastic compared with glass is also based on an unknown number of experiments, Wall et al (1953) found that red cells survived in vitro less well when stored in plastic than when stored in glass

Walter et al (1957) have obtained 28-day survivals that correspond closely to those reported here and have claimed enhanced survival However, without direct comparison between plastic and glass storage such a claim is difficult to substantiate, and the results of the present investigation suggest that, for all practical purposes, at the end of 28 days red cells stored in glass survive as well and are as satisfactory for expansion of red-cell volume as those stored in plastic

Summary

A plastic bag for storing and transfusing blood was subjected to clinical trial

Its performance for routine purposes was in no respect superior to that of the conventional system, but its routine use would confer minor advantages such as freedom from the danger of air embolus

The post-transfusion survival of red cells was not improved by storage in plastic bags

We wish to thank the blood-transfusion research committee of the Medical Research Council for advice on planning the trial, and Prof John Bruce for support and advice

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BASAL METABOLIC RATE IN OLD MEN

AND RELATED DATA

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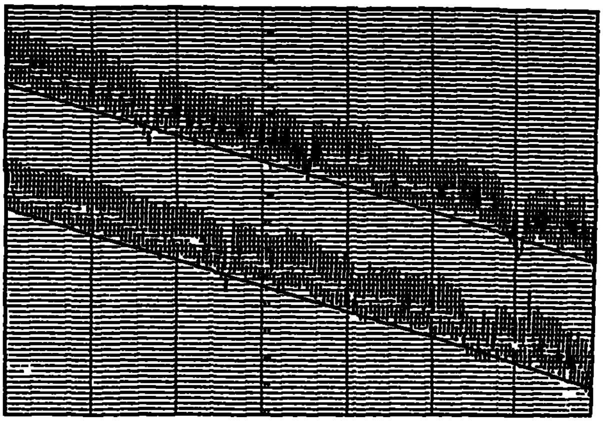
There are very few records of the basal metabolic rate (B M R) of healthy men over the age of 90 years in fact I have traced only two Benedict and Root (1934) and Benedict (1935) studied one subject aged 91, and Kise (1932) studied a Japanese aged 93 As Benedict (1935) put it " The difficulties in studying the metabolism of normal people of advanced age can hardly be overestimated Complete co-operation from the subject is necessary and a hospital environment is prohibited—both features that contribute to increase the difficulties of securing suitable subjects " For that reason, Benedict said, no further study of elderly men by the Nutrition Laboratory was planned Aub and Du Bois (1917) could find no suitable subjects between 90 and 100 years old



Basal metabolism chart of the centenarian (subject E)

I have studied five normal, healthy men aged between 90 and 100 All were living at their homes, were ambulant, were leading perfectly normal lives, and were not under any form of medical treatment For example, one was paying regular visits to his several clubs in London, one was speaking at city dinners, and the other three took regular exercise by daily walks All of them co-operated excellently during the investigations Three took transport to the metabolism department for the determination, and the other two were seen at their homes because they preferred to continue their custom of having breakfast in bed! The standard technique of measuring the B M R —as described by Robertson (1944)—was strictly adhered to The results are given in the table

In 1952 Robertson and Reid gave prediction tables for the expected mean heat-output in calories per square metre body surface per hour, and for men over 41 gave this formula 37 405365 minus 0 06944 × age in years For a person aged 95 (the mean of the series) this would give an expected mean of 30 8 calories per square metre body-surface per hour, compared with an observed value of 29 5

During the second metabolism reading, the pulse-rate of each subject was taken several times, after he had been at rest for at least forty minutes, and the lowest rate was recorded The blood-pressure was taken after each subject had been at rest for at least fifty minutes and after the metabolism readings were completed

Subject	Age	Height	Weight	Basal pulse-rate	Basal blood-pressure	Respiration-rate	Heat production (calories per 24 hr)			Heat production (calories per sq m body surface per hr)
							Total	per kg	per sq metre	
	(yr)	(cm)	(kg)	(per min)	(mm Hg)	(per min)				
A	91	165	54 3	62	125 75	8	1073	19 7	673	29 1
B	93	154	42 7	70	230 105	20	1055	24 7	765	31 8
C	95	168	56 3	60	160 95	14	1166	20 7	715	29 8
D	97	168	59 5	52	200 105	17	1120	18 8	666	27 7
E	100	160	67 3	62	190 105	21	1220	18 1	718	29·9
Mean	95	163	56 0	61	181 96	16	1127	21 1	705	29 5

Data on standard or basal blood pressure and pulse rate, as presently described, will be reported later on the Robertson and Reid B.M.R. standards (1952) which range from the ages of three to seventy-five years.

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SICKLE-CELL TRAIT IN CENTRAL INDIA

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The incidence of the sickle-cell trait in non-Negroid ethnic groups of different parts of the world appears to be higher than was thought. The trait has been found in countries bordering the Mediterranean as well as in parts of the Middle East (Lehmann 1954).

In India the sickle-cell trait has been noted in various regions. Lehmann and Cutbush (1952) reported, and Buchi (1953) confirmed, its presence in the Veddoids of South India. Sukumaran et al. (1956) found it in tribes of Western India, and Foy et al. (1956) in certain tribes of Eastern and Southern India. Stray cases have been reported from Assam (Dunlop and Mozumdar 1952) and Uttar Pradesh (Bhatia et al. 1955).

Having come across several cases of sickle-cell disease, in quick succession, in Nagpur and surrounding areas, we tried to find out the local incidence of the trait.

Materials and Methods

As a first step, a survey was made among the adult labourers of the Model Mills, Nagpur. The people examined were selected at random, except that an effort was made to ensure that no two of them belonged to the same family. The labouring population hails from different districts within a hundred miles of Nagpur. In all, 1010 persons were examined.

The presence of sickling was demonstrated by the method of Daland and Castle (1949). Fresh reducing solutions were made daily, and preparations were examined within two hours. All positive cases found on one day were re-examined the next day to eliminate false positives. Dried and stained smears of peripheral blood were examined in all cases for morphological abnormalities of red cells and for target cells. In cases showing target cells in dried smears and sickling in a wet sealed preparation, hæmoglobin analysis was done by paper electrophoresis and by alkali denaturation for confirmation.

The results of the survey are given in the table.

Most of the 1010 persons examined belonged to the local Marathi-speaking population. Sickling was present in Mahars, Kunbis, and Telis. The other groups—Gond, Koshti, Brahmins, Mohammedans, and miscellaneous groups including various other castes—did not show sickling. In Mahars the incidence of sickling was 22·2% and in Kunbis and Telis 9·4% and 11·3% respectively. Paper-electrophoretic studies in positive sickling cases showed the AS pattern, confirming the presence of sickle-cell hæmoglobin in the heterozygous form.

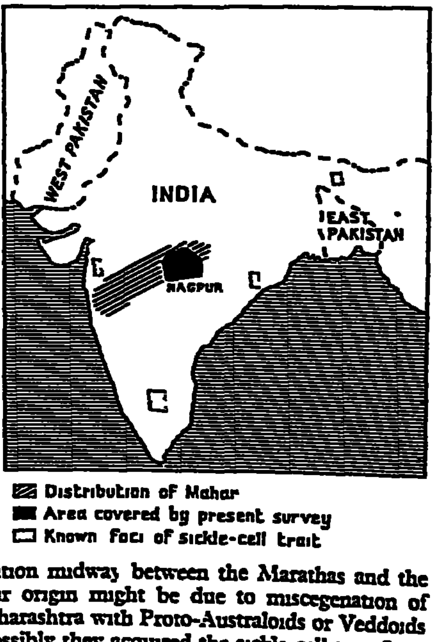
INCIDENCE OF SICKLE-CELL TRAIT IN CENTRAL INDIA

Caste	No. of persons examined	No. of persons positive for sickling	Incidence of sickle-cell gene
Mahar	450	100 (*22·2%*)	0·12%
Kunbi	116	11 (*9·4%*)	0·05%
Teli	80	9 (*11·3%*)	0·06%
Koshti	46	0	
Gond	53	0	
Mohammedan	68	0	
Brahmin	26	0	
Miscellaneous	171	0	
Total	1010		

Discussion

The high percentage of the sickle-cell trait in certain tribes of India is of interest. It is generally agreed that the sickle-cell trait was not brought to these tribes by Negro-immigration. On the presence of the Negro race in India in prehistoric times conflicting views are held. Judging from the tribal population of the present day there is no weighty evidence in support of a Negro admixture. Most anthropologists agree that the earliest inhabitants of India were Proto-Australoids. There is evidence that, in the Western coastal region, some infiltration of an African element took place during the 8th to 10th century A.D. (Mozumdar 1944). But these involved only local mixing. They were Mohammedans, and it is not yet established what kind of Africans they were. For instance, if they were Somalis they would have been unlikely to have carried the sickling gene (Lehmann 1954). Had there been a generalised assimilation of a Negro immigrant population in India, characteristic features would be met with more often in all parts of the country. The presence of the sickle-cell trait in various regions of India therefore cannot be due to mixture with Negroid blood.

The Mahars, in whom we have demonstrated the sickle-cell trait, are widely spread in Maharashtra (see figure) and speak Marathi. They are included in the scheduled castes and are hereditary village servants doing menial work. Owing to modern industrialisation they are now concentrated mostly in the cities and are employed in textile mills and other industries. On the basis of anthropometric measurements they appear to be a mixed community occupying a position midway between the Marathas and the primitives. Their origin might be due to miscegenation of primitives of Maharashtra with Proto-Australoids or Veddoids of the South. Possibly they acquired the sickle-cell trait from the Veddoids in prehistoric times. The habits and customs of Mahars do not preclude the possibility of such infiltration of Veddoid blood.



WEST PAKISTAN
INDIA
EAST PAKISTAN
NAGPUR
▨ Distribution of Mahar
■ Area covered by present survey
☐ Known foci of sickle-cell trait

The Kunbis and Telis are different castes of Marathas. The caste status depends mainly upon the occupation followed. Kunbis are mainly agriculturists, and Telis are oil-pressers. According to Karvey and Dandekar (1951) both belong to mesocephalic elements which came to India from the North-

West and settled in the broad fertile valleys of Central Maharashtra Anthropologically they are totally unrelated to the dolichocephalic Veddoid or Proto-Australoid primitives of South India

The presence of the sickling trait in these castes is thus of great interest and raises important questions as to the method by which they acquired it Normally social customs are such that they could not have got it from Mahars, and their origin from the Northern immigrants shows that the trait is not derived from their main ancestors An independent mutation can always arise, but otherwise the only possibility left is that Veddoid blood may have found its way into these people in the same manner as to the Mahars, or, in South India, to the Todas and Badagas A similar explanation of the presence of the sickle-cell trait in Mediterranean people is suggested by *Lehmann (1953)* Extensive anthropological studies about the presence of any Veddoid features in these people will be of great interest It is now clear that the sickle-cell gene protects in some degree against the more severe effects of falciparum malaria If the gene was introduced into an endogamous community by even a few individuals the gene frequency could have risen with every succeeding generation as the result of a slightly higher malarial mortality of the non-sicklers

Summary

At Nagpur 1010 adult labourers of different castes were examined for the sickle-cell trait

In the Mahars, Kunbis, and Telis its incidence ranged from 9 4% to 22 2%

It is highly improbable that this trait was brought to India by Negroes from Africa More probably the present population acquired it from the primitive Veddoids or Proto-Australoids

We wish to thank the management of Model Mills, Nagpur, for permitting us to undertake this study, and we are indebted to Shri B A Sathe, labour welfare officer, Model Mills, and to Dr J Sood and Shri D N Hakim, without whose help it would have been impossible to complete the study for technical help, our thanks are due to Shri V G Jog Prof J B Shrivastav, of the Medical College, Nagpur, and Dr P M Bhandarkar, the dean, have authorised publication of this report The survey was conducted with a grant-in-aid from the Indian Council of Medical Research

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Preliminary Communication

INTRARENAL VARIATIONS IN HÆMATOCRIT

The whole-body hæmatocrit is lower than that of the blood in large vessels, and the hæmatocrit in the kidney has been found to be only a third to a half of that in the large veins [1] [2] Fahræus [3] showed that, because of axial streaming of corpuscles, blood flowing through smaller tubes contains a higher proportion of plasma This "streamlining" effect on small-vessel hæmatocrit has been regarded by Pappenheimer and Kinter [4] as not adequate to explain fully the low hæmatocrit observed in the kidney, and they have suggested that the series of glomerular afferent vessels coming off the interlobular arteries constitutes an apparatus for drawing off the cell-poor peripheral layer of blood—a "plasma-stripping" effect, in consequence of which the juxtamedullary glomeruli would receive blood of low hæmatocrit, while the outer glomeruli would receive blood of progressively higher hæmatocrit Since the blood supplied to juxtamedullary glomeruli pursues a later course separate from the cortical circulation,[5] it appeared of interest to see whether the hæmatocrit differs substantially in different zones of the kidney If streamlining were the predominant mechanism, the hæmatocrit would be low in zones containing many small vessels, whereas Pappenheimer's plasma-stripping effect would allow of the occurrence in quite large vessels of blood of low hæmatocrit, determined by its site of origin in the juxtamedullary glomeruli

INVESTIGATION

Methods

After exposure and gentle freeing of the kidneys and renal pedicles under pentobarbitone anæsthesia, dogs were given intravenously a suspension of their own erythrocytes, previously labelled with ^{32}P, in saline containing ^{131}I-labelled human plasma-albumin After ten minutes to allow adequate distribution of the injected cells and albumin, a blood sample was taken, the renal artery and vein were simultaneously ligated and divided, and the excised kidneys were frozen in a CO_2-ethanol mixture The renal pelvis was then cut away to expose the tip of a papilla, and a core of kidney from papilla to cortex was removed in a cork-borer The frozen core was extruded by a screw, and serial sections 1–2 mm thick were placed on plastic discs and weighed The amount of ^{32}P and ^{131}I in each slice was calculated after appropriate radioactivity measurements, and the relative amounts of ^{32}P and ^{131}I in the sample of venous blood were also determined From these results was calculated for each slice the hæmatocrit percentage $^{32}P/(^{32}P+^{131}I)$, and the "vascular volume" (sum of the spaces occupied by cells and plasma)

Results

Our findings will be reported in detail elsewhere, but the general pattern is shown in the figure, which represents the mean results obtained from 13 kidneys treated in this way (single kidneys with thin slices from 5 dogs, both kidneys with thicker slices from 4 dogs) The hæmatocrit in each zone has been expressed as a percentage of the large-vessel hæmatocrit of the dog from which the kidney was taken The inner zone of cortex contained blood whose hæmatocrit was significantly higher than that in the outer zone of cortex ($P<0\ 01$), and the blood in the cortex (both zones) was of higher hæmatocrit than blood in the medulla ($P<0\ 001$) For the series of 13 kidneys, the corticomedullary hæmatocrit difference was positively correlated with the difference in hæmatocrit between inner and outer cortex The differences in hæmatocrit were not related to variation in "vascular volume" or to the presence of visible large vessels

DISCUSSION

The observation that the hæmatocrit is lower in the outer cortex than in the inner cortex can probably be explained by the preponderance in the outer cortex of small vessels, in which streamlining alone would lead to a low hæmatocrit. Our observations on the distribution of hæmatocrit within the cortex clearly give no support to the view that because of plasma-stripping the more superficial glomeruli receive blood of high hæmatocrit, but equally they do not exclude this possibility, since the technique used cannot differentiate between the small amount of blood in the glomeruli and the much larger amount in the peritubular capillaries

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1 Gibson, J G, Seligman, A M, Peacock, W C, Aub, J C, Fine, J, Evans, R D *J clin Invest* 1946 25, 848
2 Allen, T H, Reeve, E B *Amer J Physiol* 1953, 175, 218
3 Fahræus, R *Physiol Rev* 1929 9 241
4 Pappenheimer, J R, Kinter, W B *Amer J Physiol* 1956 185, 377
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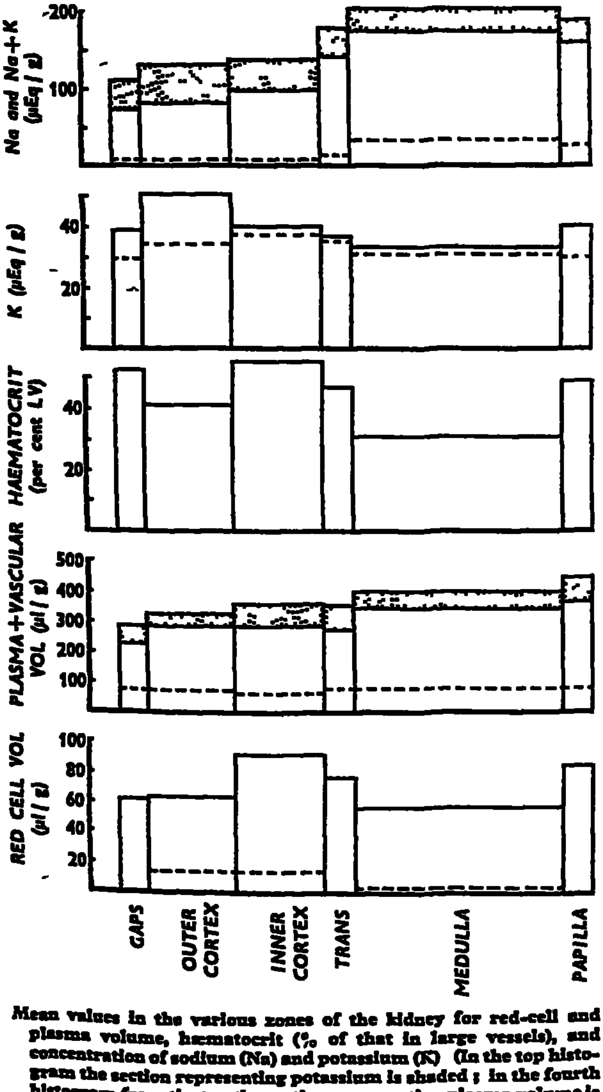
Our finding of a low hæmatocrit in the medulla seems to us much more conclusive evidence that streamlining effects must be supplemented by plasma-stripping effects, as suggested by Pappenheimer The vasa recta of the medulla are large vessels, and so might be expected to contain blood of a relatively high hæmatocrit, our finding that the hæmatocrit in this zone is in fact the lowest in the kidney suggests that these vessels have been supplied with blood which was of low hæmatocrit right at its source from the interlobular arteries We think that this finding supports Pappenheimer's view that blood of low hæmatocrit is drawn off into the juxtamedullary glomeruli, from which the vasa recta are supplied

Since red cells perfuse the kidney more rapidly than plasma, and since the renal-vein hæmatocrit is similar to the renal-artery hæmatocrit, the existence of a (predominantly) plasma shunt must imply the existence elsewhere of a (predominantly) red-cell shunt This might be no more than the fast axial stream in a multitude of small vessels, or it might be a smaller number of large communications such as permit the passage of glass beads of up to 180μ diameter[7] Our results cannot discriminate sufficiently between these alternatives, but the finding of a higher hæmatocrit in the inner than in the outer cortex might suggest that the inner zone of cortex contains high-hæmatocrit arteriovenous shunts There is a possible anatomical basis for this view in the large vessels of the "arcuate sponges" in this region[8]



Mean values in the various zones of the kidney for red-cell and plasma volume, hæmatocrit (% of that in large vessels), and concentration of sodium (Na) and potassium (K) (In the top histogram the section representing potassium is shaded ; in the fourth histogram from the top the section representing plasma volume is unshaded.) The distribution of hæmatocrit is discussed in the text ; the high concentration of (Na+K) in the medulla confirms the findings of Ullrich and Jarausch.[6]

The broken line across the histograms for Na, K, plasma, and red-cell volume indicates the amounts remaining in a kidney which had been perfused at a pulsatile pressure of 130/80 mm Hg for ten minutes with salt-free 6% dextran In the various zones of this kidney, differences in "apparent extravascular albumin" were insufficient to account for the differences in apparent hæmatocrit found in the series of other kidneys

Caps.=capsule. Trans =transitional zone

Our main finding, however, is that the medulla contains low-hæmatocrit blood, though from the large size of its vessels blood of high hæmatocrit might have been expected This finding is most easily explained on Pappenheimer's hypothesis that low-hæmatocrit blood is "stripped off" into the proximal branches of the interlobular arteries to supply the juxtamedullary glomeruli (and hence the vasa recta of the medulla)

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Reviews of Books

Burns Pathology and Therapeutic Applications

Simon Sevitt, M D , M SC., F R.C.P I , consultant pathologist to the Birmingham Accident Hospital and M R.C. Burns Research Unit. London Butterworth 1957 Pp 364 37s 6d

Burns may kill in various ways and postmortem examination often shows little macroscopic evidence of the immediate cause of death, apart from the local lesion Peripheral circulatory failure, electrolyte disturbance, damage to kidneys, lungs, brain, or other tissues, ill-advised fluid replacement, toxic absorption of local applications, bacterial infection these and many other factors may be involved During the past twenty years much has been learned about these matters and many detailed studies are scattered through the world's literature Dr Sevitt is to be congratulated on collecting and collating this mass of information and condensing it into a book of readable size He has had wide experience as pathologist to the M.R C Burns Research Unit in Birmingham, and the addition of his own observations and experimental work make this a book of exceptional merit for the first time in English a detailed discussion of all branches of the pathology of burns appears in a single volume The book is divided into three sections the local pathology of the skin, the mortality and causes of death, and the pathology of various systems and organs There are also additional chapters on burns from other causes, including irradiation

Many more patients with extensive burns now survive the shock phase only to die during the subsequent weeks, and it is during this period that the mortality-rate can still be reduced The first requisite is a thorough knowledge of the complex changes in function which follow burning, and Dr Sevitt's book presents the available information clearly and concisely It should be widely read by all those who have to deal with these perplexing cases

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[6] Ullrich, K. F., Jarausch K. H. *Pflüg Arch ges Physiol* 1956, 262, 537

[7] Simkin B., Bergman, H. C., Silver, H., Prinzmetal, M. *Arch intern Med* 1948, 81 115

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The Clinical Application of Hormone Assay

JOHN A. LORAINE, M B, PH D, M R C P E, member of scientific staff, clinical endocrinology research unit (Medical Research Council), University of Edinburgh Edinburgh and London E & S Livingstone 1957 Pp 368 30s

THIS book has three purposes to review existing methods of hormone assay, to discuss their clinical application, and to suggest lines for future application The result, however, is largely a discussion on methodology for the assay of pituitary, placental, adrenal, and gonadal hormones, with a brief chapter on insulin The thyroid and parathyroid hormones are not considered

The chapters on general principles in hormone assay and on pituitary gonadotrophins are particularly valuable, reflecting as they do the careful work of the Edinburgh group The clearly written introductions to the other chapters are also helpful Much space is devoted, however, to methods no longer in use and now only of historical interest The present trend is to progress from bioassay to chemical methods and from relatively non-specific to more specific chemical procedures In the corticosteroid chapter, for example, the cold-protection and mouse eosinophil tests could have been omitted, and methods for determining reducing or formaldehydogenic steroids curtailed to give space for a more critical discussion of the methods of Norymberski

Compared with methodology, much less space is devoted to clinical application In part this is due to the inevitable delay in collecting results obtained with the newer and more reliable methods (as Dr Loraine emphasises, their future application to clinical problems will be awaited with interest), but it is also partly the result of leaving out a good deal of published data which the clinical reader might expect to find in a book of this title

The Truth about Cancer

CHARLES S CAMERON, M.D London Hutchinson Medical Publications 1957 Pp 256 30s

Cancer and Common Sense

GEORGE CRILE, Jr, M.D London Robert Hale. 1957 Pp 143 10s 6d

THE book by Dr Cameron, who is medical director of the American Cancer Society, was written for the laymen of that country, and its style will be less familiar to British readers There is a great amount of technical detail (the index lists almost a thousand topics) and some of the headings (retinoblastoma, acid phosphatase, and xeroderma, for example) seem a little incongruous in a "popular" book But it is very lucidly written, and its object is clear enough—the patient must be warned of the significance of certain "danger signals" and encouraged to act on them

Cancer and Common Sense is also from an American pen, but it is written with the British reader in mind (there are references to the National Health Service) and it is likely to be widely read in this country Despite its brevity and simple style, it represents one of the most adult approaches to the subject yet published Dr Crile pays the reader the compliment of telling him some of the facts about cancer from which the layman is often shielded "Our present diagnostic tests are totally inadequate to detect internal cancers at a stage in which they can often be cured" A study of doctors suffering from cancer showed that delay in diagnosis would not be appreciably reduced "if everyone could be sent for four years to medical school" And Dr Crile observes that at least one series of cases has been published which suggests that "it has not been proved that the survival rate of patients with cancer of the breast, using the five year survival as an index, is affected by treatment at all"

Someone who reads this book immediately after Dr Cameron's may be pardoned for feeling a little confused But he will be heartened, not depressed, by Dr Crile's frank appraisal, for much of the fear which the word "cancer" inspires is fear of the unknown

Color Atlas of Dermatology

Chief editor GIICHIRO HARADA, M.D, professor of dermatology, Tokyo Medical and Dental University Tokyo Kanehara Shuppan London H K Lewis 2 vols Pp 100 £11 each

THIS work contains about 200 colour photographs, mostly of full-plate size, depicting skin eruptions in Japanese There are also some smaller plates, including a few photomicrographs The material was selected by six professors from 2500 photographs submitted from 31 clinics throughout Japan Ten-line captions give clinical and laboratory findings, which are often superfluous

The pictorial standard is variable yellows are overemphasised, and definition has sometimes been lost through overmagnification from transparencies or imperfect alignment of blocks The choice of subjects is not always happy it is unprofitable to diagnose malignancies at such an advanced stage as is here represented, and some other conditions, although interesting to the specialist, are so rare as to be out of place in a relatively small collection An index covering both volumes appears at the end of the second Some of the material may be of value in postgraduate teaching

The Collected Papers of Hugh Trumble

Editors LEONARD COX, M.D, R S LAWSON, F R C.S, T E COWE, M D Alfred Hospital, Melbourne, in conjunction with Melbourne University Press 1957 Pp 302 84s

MOST British surgeons know Hugh Trumble as the originator of a method of arthrodesing the hip-joint by an extra-articular bone-graft (This procedure was the basis upon which the late H A Brittain developed his operation, which is probably more widely practised today) But Mr Trumble has achieved eminence in several spheres besides that of orthopædics, as the many topics covered in this volume testify In particular, he has won fame as a neurosurgeon, and his work on the autonomic system has commanded wide attention

This book gathers together 26 papers published during the last thirty-five years The practical value of some, notably those concerned with bone and joint tuberculosis, has decreased with the passage of time others, such as that describing the angiomatous malformations of the brain, are of enduring interest Together they make an interesting and instructive tribute to a surgeon who "specialised" in many ways

Tumor Surgery of the Head and Neck

ROBERT S POLLACK, M D, F.A C.S, clinical instructor in surgery, Stanford University School of Medicine London Henry Kimpton 1957 Pp 101 37s 6d

"HEAD and neck" was, and probably still is, the anathema of the anatomy student because of its intricacies and the feat of memory involved in their command, so it is only on anatomical grounds that a specialty of head-and-neck surgery has arisen, for there is no biochemical nor physiological denominator to give it logic and we suspect that it becomes the special province of those who delight in anatomical dissection—partly through the default of those who do not The mutilations required in radical cancer surgery of the neck and head are adequately described The cancerous lesion most commonly requiring treatment in the head and neck must be epithelioma of skin or buccal mucous membranes, including the tongue, and while radiotherapy remains the chief method of treating it in this country this book's appeal will be limited

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A Handbook on Diseases of Children (8th ed Edinburgh E & S Livingstone 1957 Pp 483 27s 6d)—The new edition of Dr Bruce Williamson's elegant and handy volume is welcome, for it is concise, easy to read, and packed with information Recent advances have been incorporated and this edition is as up to date as a yearbook Some of the illustrations have an antique charm which reminds us not only of the pædiatrics of bygone days but also of the great improvements in clinical photography We cannot wholly suppress the hope that they will be retained Perhaps the reproduction of some of the radiographs could be bettered for the next edition

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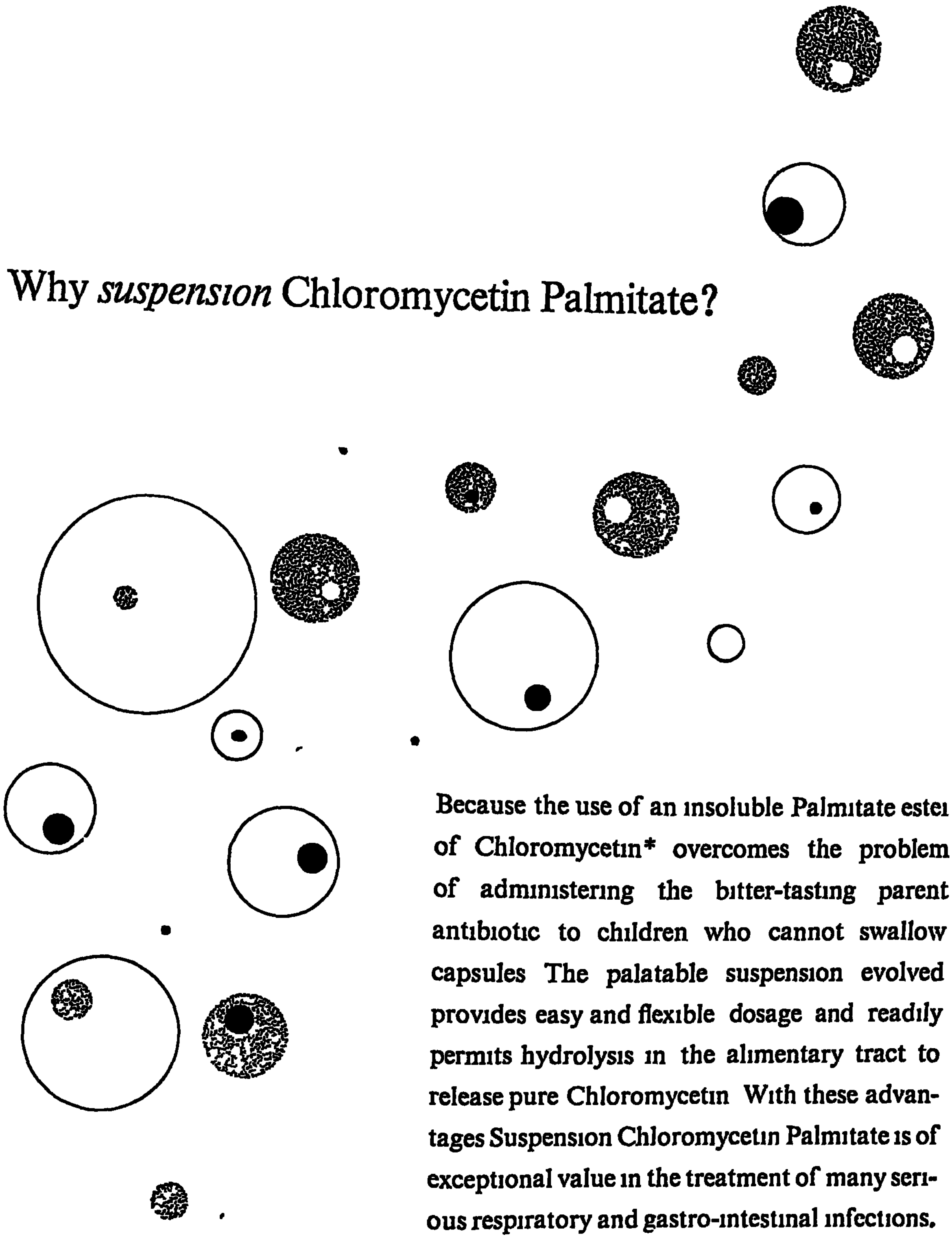

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THE LANCET

LONDON 8 FEBRUARY 1958

Septic Surgery

AN expert in any job needs first-class equipment **HERMANN GEIGER** is an expert who lands aeroplanes, for rescue purposes, on Alpine slopes This, like a surgical operation, is difficult and dangerous Mr **GEIGER**, though he naturally likes to have his aeroplane in perfect condition, says that "Accidents are caused by imprudence or clumsiness of the pilot Discipline in the Alps must be extreme"[1] There is a lesson here for those of us who practise surgery and its allied skills Much has been lately said about the buildings and equipment needed to prevent infection of surgical wounds Indeed, medical administrators cannot escape some responsibility for the present frequency of wound sepsis until better conditions for surgery have been provided, but this does not mean that those who need these facilities should meanwhile blame their tools and disclaim responsibility for accidents

Modern studies on the bacteriology of air encourage surgeons to ask for pressure-ventilation equipment in their operating-theatres This greatly reduces the risk of airborne infection, but even without it a surgical team can do much to reduce that risk Important sources of infection in the theatre are unsterilised fabrics, especially blankets, and clothing which, even through a surgical gown, scatters contaminated particles when the wearer moves Few surgeons now allow woollen blankets in their theatres, and some demand abolition of these insanitary objects from the wards as well Yet we still see in the theatre people who have not changed from their ordinary clothes or uniform into clean theatre garments before putting on a gown Many hospital workers are carriers of *Staphylococcus aureus*, and **HARE** et al[2, 3] now find that some of these are especially active "shedders" from whom staphylococci pass through clean clothing and contaminate the surrounding air Professor **HARE** has shown, too, that the perineum is a serious source of staphylococci from people who do not carry this organism elsewhere Regular tests to reveal carriers and shedders may not appeal to many members of the theatre team, who should, then, not omit a bath or shower as an immediate preliminary to every day's work During most operations activity is great, nurses and anaesthetists hurry to and fro, and in a recent symposium on hospital infections **BLOWERS**[4] noted that often 50 or 60 exits are made from the theatre during an operation Correction of these and other faults reduced the risk of airborne infection almost as much as did the installation of a new ventilation system, and the two measures together reduced the risk further than had either alone It is, then, a surgeon's responsibility to make no incision until everyone in the theatre is properly clothed and preparations are such that no-one need leave the room during the operation Whatever may be the risk of infection from a *Staph aureus* carrier it is greatly exceeded by that from an actual lesion A purulent lesion on the hand or forearm is an absolute bar to any "scrubbed" duty at an operation

HOWE[5] reminds us that "Wound suppuration is the septic decomposition of necrotic tissue, blood clot or serum Wounds closed with accurate hemostasis, without tension or dead space and with a minimum of crushed cells, seldom become infected " He also underlines the need to segregate patients whose wounds, despite these precautions, become septic Barrier nursing has seemed of little value in recent outbreaks, and when separate accommodation is provided, as it should be, it must be used even for trivial sepsis despite the inconvenience

The revelation by **BOWIE**[6] that 90% of Britain's sterilising equipment is out of date may lead to many demands for replacement Yet much of this equipment is capable of effective sterilisation if loaded with properly packed containers and operated by staff who understand how it works as well as knowing which knobs to turn Few surgeons or theatre sisters could read a recent textbook on sterilisation[7] without becoming aware of some defect in their existing procedures Claims for new autoclaves are hardly justified unless existing equipment is being properly used and its inefficiency is confirmed by reliable tests Laboratory tests of sterilisers are not as simple as was once believed But **HOWIE**[8] has given clear advice on these, and Dr **KELSEY**, whose article appears on p 306 this week, finds as did **HOWIE**, that a chemical indicator is preferable to bacteriological examination in testing for spores

Some of the procedures we have discussed involve breaks with familiar ritual Every surgeon expects to change his operating technique to take advantage of improvements that come to his notice, and there is no reason to adopt a different attitude to aseptic techniques Many discoveries that influence the practice of asepsis are made in subjects that rarely come to the notice of a busy surgeon This difficulty can be overcome by the creation of local cross-infection committees composed of surgeons, physicians, anaesthetists, bacteriologists, and nurses who will consult, when necessary, the hospital engineers, administrators, and architects, the Public Health Laboratory Service, and the medical officer of health if these are not already represented on the committee The duty of such a committee is to collect information on the frequency of hospital infection, and on local defects of equipment and procedure, and to make suggestions for improvement No conscientious clinician will regard this as interference with his right to choose his own methods He will bring his problems to the committee and offer it advice based on his own experience An energetic committee will find no shortage of work

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[1] Observer, Jan. 26 1957
[2] Hare R. Thomas C. G A. *Brit med J* 1956, ii 840
[3] Hare R. Ridley M *Brit med J* Jan 11, 1958 p 69
[4] Blowers R. in Hospital Coccal Infections a symposium arranged by the Association of Clinical Pathologists In the press
[5] Howe, C. W *Ann Surg* 1957 146, 384
[6] Bowie J H *Pharm J* 1955, 174 473 489
[7] Perkins J J Principles and Methods of Sterilisation. Oxford, 1956
[8] Howie J W., Timbury M C. *Lancet*, 1956, ii, 669

Tuberculosis and Physique

MANIFEST tuberculosis is likelier to develop in tall thin men than in short fat ones [1] [2] PALMER et al [3] have studied the incidence of tuberculosis in more than 68,000 Navy recruits in the U S A for an average period of four years after admission to a training-centre Tuberculin skin tests were undertaken at the start of the period in all of them, and the height and weight of a random sample of 1138 were also known Among this sample the distribution by height and weight of the group with tuberculin skin sensitivity did not differ materially from that of the group without it, and those with large reactions had much the same body-build as those with small ones The presence or intensity of sensitivity appeared, therefore, to be unrelated to height or weight But the incidence of manifest tuberculosis in the next few years was much greater in tall men and in those considered underweight Thus the annual rate per 100,000 was 63 for men 6 feet or more in height, but only 21 for those less than 5 ft 6 in , it was 30 for the group within 5% of the " standard " weight for their height, and 75 for those 15% or more underweight As in an earlier study,[4] the rates were much higher among those with tuberculin skin sensitivity at the start than among those without this—157 among positive reactors and only 29 among non-reactors In the reactors the annual rates for the four years were much the same, indicating an almost uniform incidence of extension of disease, but in the initial non-reactors the rates rose from 6 per 100,000 in the first year to 40 in the fourth—an expression of the cumulative risks of becoming diseased and of the disease extending

It is, of course, not surprising that the risk of tuberculous lesions being discovered clinically or radiographically is greater in those with tuberculin-sensitive skins, for it seems probable that in most cases a positive tuberculin reaction indicates the presence of living tubercle bacilli in the body, and it is to be expected that, in circumstances where the risk of infection is small, more of the already infected should become manifestly diseased The distinction between the " infected " and the " diseased " is indeed an artificial one A person infected with tubercle bacilli is, according to the recognised, though ill-defined, meaning of the word, " diseased " When infection was almost universal in adults and " disease " was recognised only by clinical means, it was convenient to separate the clinically well from the clinically unwell and call the one " infected " and the other " diseased " Later, with radiology, it became possible to distinguish among the clinically well a group with radiographic abnormalities, and these also became " diseased ", the residuum of the " infected " now containing those with positive skin tests but without discovered lesions This classification sufficed as long as there was no means of preventing the " infected " from becoming " diseased ", other than by raising or maintaining the general level of nutrition—turning tall thin men into fat ones Now, however, antibacterial drugs offer at least a possibility of preventing extension of lesions, and even of killing all the bacilli in them There may, therefore, be a case for classifying all those infected with tubercle bacilli as diseased, this would at least help to clear away some of the misleading jargon that has accumulated around tuberculosis. The " tuberculin converter " might then be recognised as one in whom tuberculous lesions have recently developed—a diseased person

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[1] Long F R , Jablon, S Tuberculosis in the United States Army in World War II an epidemiological study with an evaluation of X ray screening Veterans Administration Medical Monograph Washington, D C , May 1955

[2] Berry, W T C Nash, F A *Tubercle Lond* 1955, 36 164

[3] Palmer, C. E , Jablon S , Edwards, P Q *Amer Rev Tuberc* 1957, 76, 517

[4] Medical Research Council *Brit med J* 1956 i, 413

Sudden Deafness

THE rapid onset of severe deafness is always alarming, whether it affects both ears or only one The onset may be instantaneous, or hearing loss may progress over hours or days A roaring tinnitus may accompany the deafness, and vertigo is not uncommon Apart from the cases associated with infection of the middle-ear cleft, sudden deafness is nearly always due to affection of the neural apparatus of hearing—either the cochlea itself or the auditory nerve and its connections Toxic neuritis may be caused by any of several infections, including measles, scarlet fever, mumps, typhus, and herpes The deafness of mumps, although severe, is characteristically unilateral, and it may therefore be long unsuspected, especially in young children The origin of the deafness is further obscured when the initiating illness takes a subclinical form In otitic herpes perceptive deafness may be accompanied by other symptoms, such as earache, facial palsy, and vesiculation in and around the affected ear Nerve deafness may appear quite suddenly in suppurative labyrinthitis or meningitis, and congenital syphilis (although now fortunately rare) is a further cause Sudden deafness may also result from an anaphylactic reaction to the injection of a vaccine, and in 2 patients seen by HALLBERG [1] at the Mayo Clinic a bee-sting was thought to be responsible Transfusion with rhesus-incompatible blood has been named as a cause by FOWLER [2], and a further cause is spontaneous hæmorrhage into the labyrinth in such blood dyscrasias as leukæmia or hæmophilia A traumatic origin is usually obvious, especially where deafness follows fracture of the base of the skull Nearly always deafness from these causes is sudden, severe, and permanent By contrast the deafness of Menière's disease tends to fluctuate greatly and to take second place, at least in the patient's estimation, to the crippling attacks of vertigo Hysteria is a rare cause of sudden deafness, but its possibility should be kept in mind, especially where the deafness is bilateral Malingering should be suspected in the potential litigant, who usually feigns unilateral deafness

FOWLER remarks that sudden deafness of unknown origin is commoner, in his experience, than sudden deafness of known origin. "Sudden unilateral or bilateral impairment of hearing", says **Hallberg**,[3] "is a symptom, not a disease", and it behoves us to seek a cause, especially as treatment may succeed if the mechanism is understood and the patient is seen early. **Hallberg** records his experience of 178 patients with sudden deafness who were seen at the Mayo Clinic in the five years from 1949 to 1953. No apparent cause was found in 89 of these, all had perceptive deafness, usually of the end-organ type, with loudness recruitment. This finding is compatible with the commonly held view that most of these cases are caused by a vascular lesion, the cochlear (and the vestibular) branches of the internal auditory artery are end-arteries, and thrombosis, hæmorrhage, or vasospasm could therefore affect the sense-organ, producing total or partial sudden deafness. **Fowler**[2] noted that 77% of his patients with sudden deafness were under 40 years of age. In 23 out of 26 cases there was a history of emotional episodes preceding the deafness. Such episodes, he added, are known to affect the neuromuscular mechanisms through the responses of the autonomic nervous system, leading to vascular contraction, "sludging" of the blood, and eventually congestion, œdema, local anoxia, and leakage from the capillaries, these factors might be the cause of sudden deafness. **Lindsay** and **Zuidema**[4] described a further 16 cases in only 4 of which the cause was known. In the majority of the remaining 12 cases both auditory and vestibular functions were involved, several of the patients were under the age of 30. **Lindsay** and **Zuidema** concluded that vascular occlusion was an unlikely cause. On the other hand, **Moulonguet** and **Bouche**[5] described a single case in which the evidence of vasospasm was strong. Deafness developed suddenly in the right ear of a young man a few hours after he had received an injection of an "orthobiotic" serum. Four days later an audiogram showed a loss of 65 decibels, in the speech range, in the affected ear, the Rinne test was positive and recruitment was demonstrated by Fowler's binaural loudness-balance test. On the assumption that the deafness was due to arteriolar spasm, the patient was given sodium nicotinate intravenously. Peripheral congestion followed, and three hours later the hearing returned to normal. Of the 89 patients with sudden deafness which **Hallberg** classified as probably of vascular origin, about a quarter were hypertensive, arteriosclerotic, or both, with hypertensive changes in the ocular fundi. The majority of the 89 were in the older age-group, and the age distribution accorded fairly closely with that of coronary occlusion. **Hallberg** found some evidence that such patients were abnormally susceptible to other types of vascular accident later in life.

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[1] Hallberg, O E *J Amer med Ass* 1957, 165 1649

[2] Fowler, E P *Ann Otol , &c , St Louis*, 1950, 59, 980

"In such a fine mechanism as that of the end-organ of hearing", says **Hallberg**, "irreversible changes may take place quickly." It is not surprising, therefore, that the results of treatment have been disappointing. But some hope may be held out if help is sought early. **Hallberg** recommends the administration of nicotinic acid in large doses on account both of its vasodilator effect and of its apparent tendency to reduce the blood-cholesterol level.

Annotations

RISING COSTS

Capital expenditure on hospitals is the subject which the Comptroller and Auditor General has chosen this year as the chief topic of his review of the National Health Service finances.[1] He begins by recalling that the 1956–57 estimates provided for this purpose £12½ million for England and Wales and £2¼ million for Scotland, and goes on to describe the theoretical pattern by which this money is allocated, with hospital boards seeking the Ministry's consent for works estimated to cost more than £30,000 and the Ministry seeking the Treasury's sanction for schemes costing more than £60,000. To this exposition he adds a real-life story. "Among the major works now in progress in England", he begins, "is a scheme for adaptations and new construction at a teaching hospital." He retains this discreet anonymity throughout his tale, but the more forthright methods of the daily press[2] have made it clear that in fact he is writing about the United Oxford Hospitals.

In 1955, it seems, the Treasury approved building projects for the board of governors of this hospital at an estimated cost of £434,000. By 1956 the Treasury was being informed that the estimate was now £815,000 and that the board had started "a considerable amount of work without the Ministry's prior authority". The original scheme had changed considerably, but the Ministry was satisfied that the scheme in its new form was a good one and could not be appreciably reduced in cost. The Treasury acquiesced, and the board was allowed to proceed but asked henceforth to follow normal procedure. But the latest news the Ministry had to offer was that the estimated cost had risen to £1 million, and that the board had again accepted a contract for work not approved by the Ministry. Since, however, authority would have been given, had it been sought, the Ministry sensibly did not withhold it as a result of an administrative misunderstanding.

The responsibilities and opportunities which face the Oxford board have lately been set out in the chairman's stimulating report on the future development of the hospital.[3] The Radcliffe Infirmary and its sister hospitals not only provide general medical services for 1½ million people, and specialist services, such as plastic and neurological surgery, for some 5 million, but also are associated with a rapidly expanding medical school and have to offer the new Nuffield professors facilities for clinical research and teaching.

Whatever moral the Comptroller's tale may have been intended to point, it certainly shows how difficult it is to follow a prearranged pattern in a world of rising costs and changing plans.

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[3] Hallberg O E. *Laryngoscope* 1956 66 1237

[4] Lindsay, J R, Zuidema J J *ibid* 1950, 60 238

[5] Moulonguet A, Bouche J *Ann Oto-laryng* 1952, 69, 71

[1] Civil Appropriation Accounts (Classes I–V) 1956–57 H.M Stationery Office Pp 340 20s.

[2] See *Times* and *Manchester Guardian*, Jan. 30, 1958

[3] See *Lancet*, 1957, i, 732

ALLERGY TO COW'S MILK

THE symptoms of severe allergy to cow's milk are dramatic and often alarming. Many pædiatricians claim that such allergy is rare. Vendal,[1] for instance, found only 23 definite cases in the four children's hospitals in Stockholm in the years 1919–47. Others maintain that colic and vómiting in young children are often due to allergy to cow's milk.

Backman and Dees[2] have investigated the *frequency* of this disorder in young infants. They observed 403 infants attending well-baby clinics, at one year of age 360 patients were still under observation. Strict criteria were adopted. A baby was considered to be allergic only when ingestion of small amounts of cow's milk was regularly followed by (*a*) eczema, papular urticaria, asthma, or non-infectious rhinitis, or (*b*) gastrointestinal symptoms (vomiting or diarrhœa), these reactions must be reproducible on repeated exposure to cow's milk over a considerable time, and absent when there was no contact with milk. Of the 403 babies 99 were fed exclusively on breast-milk for the first month, 41 had breast-milk plus evaporated-milk supplement, and 263 had an evaporated-milk formula. After the age of one month various types of food were added to the diet. Of the 304 artificially fed infants 4 had definite allergy to cow's milk. 2 additional infants developed rashes but were not definitely proved to have allergy. The symptoms in the allergic infants were colic (2), diarrhœa (2), wheezing (1), rash (1), frequent "colds" (2), they occurred alone or in various combinations. In each the symptoms were present by the age of three months, in most by the age of one month. The symptoms recurred when the milk was reintroduced into the diet. By fifteen months of age, 1 of the 4 children was being fed on cow's milk without symptoms, 1 was asthmatic, and the 2 others were having symptoms suggesting that allergy to milk was still present. 52 of the group of infants were of the crying colicky type, but only 2 of these were allergic to cow's milk. This seems to support the view of many pædiatricians that colic is only rarely due to milk allergy. Although wheezing was present in 40 of the group at some time during the first two years, this could be attributed to cow's milk allergy in only 1. Scratch tests were negative in 66 of the 72 infants tested. No correlation was noted between positive tests and allergic symptoms, 2 negative reactors had severe milk allergy. Backman and Dees point out that the results of their such tests agree with the generally accepted view that skin tests cannot be relied on to differentiate the very young allergic infant from his healthy contemporary.

Backman and Dees also studied 172 infants under two years of age referred for allergy studies during the same period. Only 109 were found to have allergic disorders. By the same criteria as in the well-baby group, 33 of the 109 were sensitive to cow's milk. Eczema was the commonest symptom due to milk sensitivity. Next in frequency were gastrointestinal symptoms. Respiratory symptoms (mild asthma and rhinitis) were least common. All the 33 milk-sensitive infants also gave positive scratch tests to milk, but 4 non-allergic infants also gave positive scratch tests. Thus in allergic infants under two years of age, as opposed to non-allergic infants, the incidence of allergy to cow's milk was high, being present in 1 in 3 patients of the series.

A comparable investigation was carried out by Collin-Williams[3] on 3000 consecutive private patients. Allergic infants or those suspected of allergy were excluded. Many of the babies were entirely breast-fed for the first few months of life. Evaporated milk was used almost exclusively for the artificially fed infants. Allergy was diagnosed on clinical evidence alone—the removal of milk from the diet producing complete remission of symptoms. Only 9 definite cases of milk allergy occurred in the 3000 cases—an incidence of 0.3%. No cases of colic attributable to milk allergy were found.

These studies indicate that in the U.S.A. milk allergy affects about 1% of infants, and that it is much more common in the frankly allergic infant. A similar comprehensive study in this country would be valuable since there is an impression that the incidence is much lower here than the American figures indicate. This might be due to the fact that the dried milks used in this country are less liable to give rise to allergy than evaporated milk.

THE CONQUEST OF MALARIA

THE history of the world has been affected by malaria on many occasions. Malaria has caused the defeat of armies—it proved a terrible ally against the Japanese in New Guinea during the late war—and it is responsible for the isolation of all but the fringes of the African continent during all historical time. The conquest of the disease is certain to have far-reaching effects on the destinies of the peoples freed from its yoke.

In an address to the Royal Society of Arts in London in December Prof. George Macdonald gave an account of the increasingly successful attempts to control malaria, and the world-wide measures which are being undertaken to eradicate it. Early attempts at control by the distribution of quinine and other antimalarial drugs failed, the discovery of the role of the anopheline mosquito and the attack on its breeding-places by drainage and spraying were the first real landmark in the conquest of malaria. The safeguarding of the Suez canal, the building of the Panama canal, and the salvation of the Malayan rubber industry were patterns for many successful (and expensive) local campaigns. The cost of operations has been greatly reduced by attacking, not the larva, but the adult mosquito with efficient insecticides. If the transmission of malaria is interrupted by killing the vector in human habitations, at the same time removing the parasites from the blood of the inhabitants by chemotherapy, the disease disappears. The mosquitoes return, but there is no malaria because there is no source from which the mosquitoes can become infected. Such a state of "anophelism without malaria" is now to be found in Crete. Control was established in 1945–48, and no spraying has been practised for the past nine years, there has been no recrudescence of malaria. It is necessary to ensure that the disease is not reintroduced to a controlled area, and Professor Macdonald emphasised the need for planning, attack, surveillance, and maintenance, the greatest care being taken to ensure continuity and efficiency at all stages of the campaign.

The discovery of strains of anophelines which are becoming resistant to the action of insecticides has made it clear that the time for an all-out attack on malaria is now. Up to the present, sixty-three countries, with a total population of 680 millions at risk, have declared their policy to eradicate the disease. In the Americas the majority of people are now protected, and malaria has virtually disappeared from the countries bordering the Mediterranean. The enormous administrative problems of control among 300 million people in India are being resolutely faced. In Central Africa a good start has been made in French and Belgian territories and in Northern Nigeria and Angola, but eradication will be troublesome and expensive because of poor communications, administrative difficulties, and special problems associated with the high intensity of transmission.

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[1] Vendal, S. *Acta pædiat., Stockh.* 1948, suppl. 5.

[2] Backman, K. D., Dees, S. C. *Pædiatrics*, 1957, 20, 393, 400.

[3] Collin-Williams, C. *J. Pediat.* 39 48

Professor Macdonald issued two salutary warnings. The first is that the amount of research devoted to the study of anopheline resistance to insecticides is infinitesimal compared with the efforts at eradication, which were inspired by the fear of it. There is need for a great deal of applied research into problems associated with the expansion of public-health programmes, and the world as a whole has not yet learned to provide it. The second warning is that the rapid increase of population in areas freed from malaria will raise new and serious problems, which are already evident in Ceylon and elsewhere. The increase is mainly to be found in rural populations, and, despite the increased area of cultivable land resulting from the conquest of malaria, a search for industrial employment is inevitable. Towns will grow rapidly, and capital investment in industry, land development, and housing will be needed on an unprecedented scale.

"The last decade," said Professor Macdonald, "has seen a greater change in the material state and outlook of people in tropical countries than any in past history. It is my conviction that this is no mere temporary surge, but the beginning of a movement which will be progressive, which will affect both tropical and temperate countries alike in many ways which may be good or bad, and which will be looked upon as one of the turning-points in the history of the world."

A MOULD FOR GOOD CITIZENS

FROM a background of centuries of living in traditional patterns, with an unchanging social framework, millions of people were uprooted during the industrial revolution and thrown into new cities. The new urban masses lost their cultural and social framework, and were left with only "their primitive obedience to unthinking instinct and their lack of any social obligation outside their narrow human circle". Making this point in his Charles Russell lecture,[1] Dr D. H. Stott said that Russell with his clubs, and his contemporaries with their schools, began to create a framework of civilisation for the youth of these urban millions. Their achievement was great (today no vast areas of our cities are unsafe for strangers), but the present resurgence of hooliganism is evidence that much must still be done. Unhappily, the youth-club movement, which is so important in this work, tends to be taken for granted and neglected by public and Government alike.

The continuation of the industrial revolution in our time is leading to increasing use of machines and automatic control, and there is less and less place for the casual labourer or the worker who prefers an occasional unpaid day at home when he feels like it. Some will deplore this tendency because it seems to subjugate the individual to the impersonal interests of social organisation, but, as Dr Stott observes, the tendency exists, and it is becoming harder for young men of low educational standard to find jobs. This is one reason for the surprising thirst among youths for the education which clubs provide, another is that "young people just tire of mere recreation". One young man came to reading-classes after his girl-friend had jilted him because of his illiteracy, another brought his girl to the club to teach her to read. In less extreme cases the clubs are often more satisfactory than the county colleges as a means of continuing education after boys and girls have left school, because the club-worker has more opportunity than the college teacher of getting to know his pupils. School-teachers have made successful club workers, and Dr Stott urges integration of the youth service into the wider educational system. The inspiration needed for club-work does not always burn for a lifetime, it should be easy for workers to enter and leave club service, and integration would help this.

Besides their stalwart work for normal, if "partially civilised", boys and girls, the clubs have done much to help delinquents. Dr Stott considered the reasons why juvenile crime persists despite better social conditions. One is that today's "rebels without a cause" stand a better chance than those of fifty years ago of surviving to rebel another day. He does not agree that their outbursts stem from social frustration when they find they cannot get on in a world where "getting on" is thought important, or indeed that they think in such general terms at all, rather they are preoccupied with the amusement of the moment and their immediate personal attachments. Their ties to their family and intimates are strong, but they do not conceive that those (outside this small circle) whom they injure may have feelings. Serious delinquency appears when some powerful disturbance of a boy's feelings towards his family has made him ignore even the harm his misdeeds will bring on them. Delinquents are not "sociological" or "psychological" but both.

Can a youth club help such boys (or girls)? By giving them occupation and recreation it removes the urge for antisocial forms of self-expression, by education and instruction it gives promise of a fuller life (and perhaps a better job), and helps remove that pattern of living by day-to-day whim which is one of the roots of delinquency. A club may well thus lead boys away from crime, but can it do anything for boys who are already hooligans? The first difficulty is to get them into the clubs, and some workers have managed this by associating with and befriending the leaders of gangs. Such leaders are rarely well-adjusted, but are usually unhappy youths needing emotional support, which a devoted, unromantic, and skilful worker can provide. Dr Stott thinks that each such worker might rescue one or two boys a year from a life of crime. A special type of club is needed for these boys, it may serve as a stepping-stone to a club of more general type. The teacher and school welfare-officer can help by spotting potential gang-leaders and criminals at an age when they are still malleable. It is extremely important that no child, however ill-behaved, should be spurned or treated as a nuisance, if he learns to regard some adult (who has made him a special responsibility) as one of his intimate circle, he is unlikely to grow up without a sense of personal obligation. If that adult is a teacher connected with a club, the association may continue fruitfully for years, even till the boy marries—yet another argument for integration of school and club.

MR. GWYNNE WILLIAMS, consulting surgeon to University College Hospital, London, died on Feb. 3.

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[1] Present Needs in our Work Among Youth. By D. H. STOTT, M.A., PH.D. Pp. 14. 9d. Obtainable from the Trustees, Charles Russell Memorial Lecture, 17, Bedford Square, London, W.C.1.

Special Articles

THE TESTING OF STERILISERS *

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Attention has been focused recently on the efficiency of hospital sterilisers (Bowie 1955, Lancet 1956) Howie and Timbury (1956) and Scott (1957) have discussed the laboratory tests they have used at Glasgow I thought it might be useful to see what information is already available about the relative thermal resistance of pathogens and of preparations commonly used for testing the efficiency of sterilisers This information from the literature is set out in table I

Thermal death times are given for each organism, representing the time required to kill a suspension of spores held at a given temperature Where the author gave a range of times, the maximum has been taken

The thermal death time was estimated by heating suspensions either in sealed glass tubes in an oil-bath (Bigelow and Esty 1920) or in an autoclave Four items (M 3, M 4, S 2, and S 3 in which the method used was not stated are cited for the sake of completeness

Only tetanus and the gas-gangrene group of organisms were included among the pathogens, because these represent the main hazard in hospital sterilisation The anthrax bacillus is comparatively sensitive to heat, and *Clostridium botulinum* is more the concern of the canning industry than of the medical bacteriologist

Table II shows the temperatures and exposure times recommended by Perkins (1956) to ensure sterility Table III gives the temperature/time characteristics of Browne's indicator tubes, type I (dressings) and type II (gloves), from data supplied by the patentee, Dr A W Chapman

Fig 1 shows the assembled data plotted arithmetically it will be seen that Perkins' safety schedule gives a reasonable margin over its rather limited range The test mesophils are quite inadequate because they are less heat-resistant than the pathogens The thermophils and soil samples range widely in their resistance from that providing a narrow margin of safety to that which would be an unreasonably exacting test for a hospital steriliser

Both types of Browne's tubes give a margin of safety, except for temperatures below 110°C This margin is wide with type-I tubes and narrower, but probably adequate, with type-II tubes

In fig 2 a selection from the same data is plotted semilogarithmically

Points representing observations on the same organisms at different temperatures are linked together This method of plotting shows that related observations tend to lie on a straight line, and that such lines tend to be parallel to each other This was first pointed out by Bigelow (1921), who found that semilogarithmic plots of the thermal death times of spores tended to have one characteristic slope and those of vegetative organisms another This relationship is widely used in the canning industry for computing heat processes The slope of the curve is usually expressed as the z value, which is the number of degrees of temperature per tenfold increase of time (Baumgartner and Hersom 1956) The z values of those organisms for which more than one observation is available are given in table I and range from 9°C to 15°C This degree of agreement is remarkable in view of the fact that the results plotted came from many authors working over a number of years and using different techniques

TABLE II—PERKINS' SAFETY SCHEDULE

Temperature (°C)	Exposure time (min)
132	2
125	8
121	12
118	18
116	30

The very careful study by Bigelow and Esty (1920) of thermophils (H 2 in table I), based on many observations, gives a z value of 10°C, this is the standard figure used by the canning industry for *Cl botulinum*, based on the work of Esty and Mayer (1922) The corresponding values for Browne's tubes are 26°C for type I and 23°C for type II Perkins' schedule does not give a linear semilogarithmic plot, but a suggested safety schedule is plotted and labelled "ideal indicator" for reasons discussed below It represents a series of time and temperature relationships which should ensure

TABLE I—HEAT RESISTANCE OF ORGANISMS

Item	No of strains	Organism	Mean thermal death time (°C per min)	Method	z value	Reference
Tetanus						
T 1	24	*Cl tetani*	100°/90, 105°/25	T	9 0	Esty and Meyer (1922)
T 2	32	„ „	95°/>60, 100 /25, 105°/10	T	12 0	Murray and Headlee (1931)
Gas-gangrene group						
G 1	1	*Cl welchii*	105°/27	T		Esty and Meyer (1922)
G 2	4	„ „	110°/10, 105°/5	T	13 0	Headlee (1931)
G 3	?	„ „	107°/5	T		Underwood (1934)
G 4	1	„ „	105°/5	A		Ecker (1937)
G 5	1	*Cl histolyticum*	105°/6	T		Esty and Meyer (1922)
G 6	4	*Cl bifermentans*	100 /45, 105°/21'	T	15 0	„ „ „
G 7	33	*Cl sporogenes*	100°/150, 105 /45', 110°/12	T	9 0	„ „ „
G 8	1	*Cl œdematiens*	110°/15	A		Ecker (1937)
G 9	1	„ „	110 /10, 115°/4, 121°/1'	A	11 0	Hoyt et al (1938)
G 10	1	*Cl septicum*	107°/5	A		Ecker (1937)
Test mesophilic organisms						
M 1	1	*B subtilis*	101°/10	A		„ „
M 2	1	„ „	100°/17	A		Schneiter and Kolb (1948)
M 3	?	„ „	104°/15	?		Perkins (1956)
M 4	?	„ „	95 /35, 100°/14, 105°/6	?	13·0	Williams (1929)
Thermophilic organisms						
H 1	?	*B stearothermophilus*	121°/12	?		Perkins (1956)
H 2	15	'Thermophils	100°/1320, 105°/690, 110 /225, 115°/84, 120 /23, 125°/8, 130 /3 5, 135 /1	T	10	Bigelow and Esty (1920)
Samples of soil						
S 1		Soil	115 /15	A		Ecker (1937)
S 2		„	100°/1020, 105°/420, 110 /120, 115°/15, 121°/6	?	9·0	Konrich (1948)
S 3		„	106°/300, 112°/60, 121 /30, 134 /10	?	•	Walbum (1931)
S 4		„	120 /20	A		Bang and Dalsgaard (1948, 1949)

T, tube method of Bigelow and Esty (1920) A, autoclave • Did not give a linear curve

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* A report to the Medical Research Council Working Party on Steam Pressure Sterilisers

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TABLE III—BROWNE'S TUBES

Temperature (°C)	Time for complete colour change (min)	
	Type I	Type II
130	6½	3½
125	10	5½
120	16	9
115	25	15
110	40	25
105	62	40
100	100	66

the death of the most resistant pathogen, with an adequate margin of safety

Experimental

It was decided not to make any further estimates of thermal death times for pathogenic organisms, because the value of such tests is limited, in that they cannot readily measure the heat resistance of spores in natural materials without losing the precision obtained by using pure cultures and known numbers of spores Furthermore, the importance of such accurate estimates is less in medical sterilisation, where a substantial safety margin must always be provided to guarantee sterility beyond reasonable doubt, than in food processing, where it is important to devise very precisely a heat treatment that will ensure a maximum proportion of sterile products with a minimum of spoilage due to overheating

It was, however, felt that a survey of the heat resistance of currently used spore preparations would be of value

A request for spore preparations was circulated to 457 pathologists in the *Weekly Summary* of the Public Health Laboratory Service 25 usable preparations were received, which make up the present series Those that were already in envelopes were tested as they were received, the rest were transferred to small envelopes made of transparent paper Tests were made by heating for various times at 100 C, 110°C, and 121°C tests at 100°C were made in a steamer, piped steam being used At 110°C and 121°C tests were made in a domestic pressure-cooker modified to receive steam under pressure from a laboratory autoclave Steam was admitted to the top of the cooker, and a continuous bleed from the bottom ensured the removal of air by adjusting its flow accurate temperature control could be obtained A mercury-in-glass thermometer was also fitted

These arrangements allowed the "come-up time" from 100°C to be less than a minute for all test temperatures

Heated spore preparations were removed aseptically and cultured in broth at 37°C for five days, doubtful tubes being subcultured to blood-agar One preparation, which contained an anaerobic spore-bearer, was cultured in cooked-meat medium for five days at 37°C and then subcultured to blood-agar aerobically and anaerobically

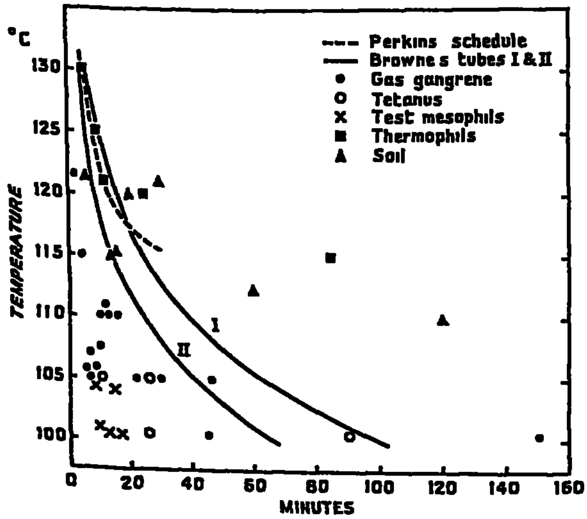

Fig 1—Thermal death times plotted from the literature

Control cultures of unheated spore preparations were set up and in each case growth was obvious overnight It was thought possible that inhibitory substances might be released from the paper or from the gum of the envelopes To test this point, at least one negative culture of each preparation was inoculated with a second and unheated spore "paper", and in each case growth took place overnight

Results

The results are listed in table IV and displayed in fig 3 Also plotted in fig 3 is the suggested safety schedule from fig 2 It will be seen that none of the preparations tested approached a satisfactory level of heat resistance

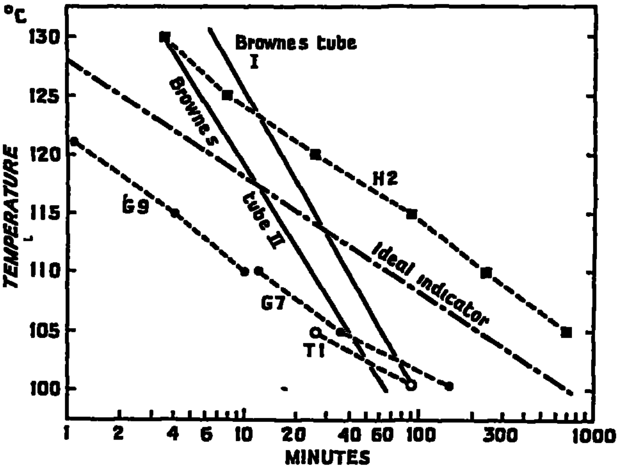

Fig 2—A selection of data from fig 1 plotted semilogarithmically

Discussion

Even with a perfectly designed and completely automatic steriliser and correctly packed loads there will always be occasions when it is desirable to test the efficiency of the sterilising process For this two methods are available—bacteriological test preparations and chemical indicators

Bacteriological Preparations

Though in theory preparations of spores provide the more realistic test, in practice the results may be dangerously misleading, unless not only the strain used but also each batch of spore papers has been tested for heat resistance Mesophils are unlikely to provide an adequate safety margin, and thermophils may be too heat-resistant and lead to the needless rejection of a sterilisation procedure Even with a preparation of suitable heat resistance there must be a delay of several days before the results are known

Soil samples are very variable, are often much too resistant, and offer certain cultural difficulties due to unidentified growth factors, if attempts are made to plate doubtful positives on to solid media (Bryce 1955)

These considerations suggest that bacteriological preparations are not suitable for routine use, and should be kept for assessing new techniques or equipment, for research purposes, and for those occasions when a rigorous "full-dress" inspection is needed for administrative or forensic reasons For such purposes only standard preparations of spores of known heat resistance should

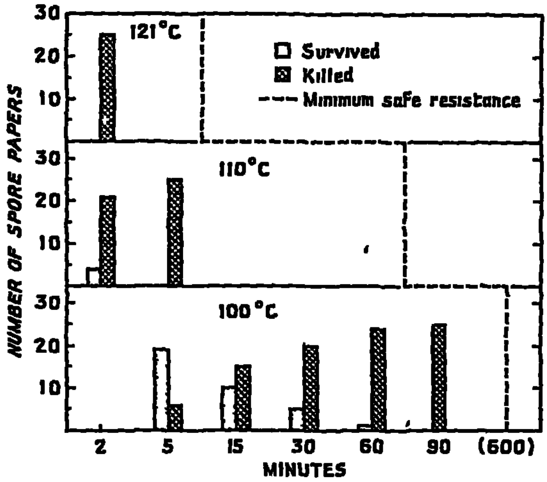

Fig 3—Heat resistance of 25 spore papers in current use for testing sterilisers *hatched*, spores killed, *stippled*, spores survived

be used, and ideally these should be provided by a reference laboratory or should be available commercially Until such standardised preparations of spores are to be had, some method of testing "home-made" ones is needed

It is easy to measure survival at 100°C by using a steamer or a boiling waterbath If a z value of 10°C is assumed and a survival of five minutes at 121°C is taken to offer a reasonable margin of safety, the semilogarithmic plot shows that a survival of six hundred minutes is to be expected If 121°C for two minutes is accepted as an absolutely minimal standard, a boiling-time of two hundred and sixty minutes is obtained It would seem, therefore, that in the absence of adequate tests at higher temperatures (which would justify the acceptance of a higher z value than 10°C) a spore preparation that will not withstand boiling for at least five hours is unsafe as a test for a sterilisation procedure

Chemical Indicators

The ideal chemical indicator should follow a temperature/time curve which runs parallel to that of pathogenic sporebearing organisms but offset by a distance which allows a reasonable margin of safety Fig 2 suggests that it should have a z value of about 10°C and should pass through, for example, the 121°C/5 min point This would give it a thermal death time of about ten hours at 100°C The indicator should show an unequivocal colour change which is completed suddenly at the end of the exposure time, and it should be stable in storage, cheap, and, if possible, sensitive only to moist heat

The one indicator readily available in this country, the Browne's tube, does not fulfil all the ideal criteria given above, in that its margin of safety is probably too wide

TABLE IV—HEAT RESISTANCE OF 25 PREPARATIONS OF SPORES

Expt no	Strain	Reputed heat resistance			Experimental heat resistance								
					100 C Min					110°C Min			121°C Min
		°C	Min	Survival	5	15	30	60	90	2	5	10	2
1	*B cereus*, p, t				– – – –	– –	– –	– –		– –	– –	– –	– –
2	*B licheniformis*, p, l				+ +	+ +	+ – + +	– – – –	– –	– – + –	– –	– –	– –
3	*B anthracoides*, c, e	100 121	30 15	K K	+ +	+ +	+ – – –	– – – –		– – – –	– –	– –	– –
4	A S B, s, e	110 115	10 5	K K	+ – – –	– – – –	– –	– –		– –	– –	– –	– –
5	A S B, c, e	110	5	S	– – – –	– –	– –	– –		– –	– –	– –	– –
6	A S B, c, e				– – – –	– –	– –	– –		– –	– –	– –	– –
7	*B subtilis*, s, l	110 115	5 5	K K	+ +	+ – – –	– – – –	– –		– –	– –	– –	– –
8	*B subtilis*, p, l				– – – –	– –	– –	– –		– –	– –	– –	– –
9	*B subtilis*, g, t				+ +	+ +	+ + + –	– – – –		+ +	– – – –	– –	– –
10	*B licheniformis*, p, e	100	60	S	+ +	– – – –	– –	– –		– –	– –	– –	– –
11	A S B, p, l	100 100	15 30	S SK	+ +	+ +	+ +	+ – – –	– – – –	+ +	– – – –	– –	– –
12	A S B, c, e				+ +	+ +	+ – – –	– – – –		– – – –	– –	– –	– –
13	*B subtilis*, p, t				+ +	– – – –	– –	– –		– –	– –	– –	– –
14	A S B, c, e				– – – –	– –	– –	– –		– –	– –	– –	– –
15	*B subtilis*, p, e				– – – –	– –	– –	– –		– –	– –	– –	– –
16	*B licheniformis* s, t	115	10	S	+ +	– – – –	– –	- -		– –	– –	– –	– – *
17	Mixed spore-bearers, g, l	121	15	K	+ +	– – – –	– –	– -		– –	– –	– –	– – †
18	A S B, p, l	130	45	K	+ +	+ +	– –	– –		+ –	– –	– –	– –
19	*B subtilis*, p, t				+ +	– – – –	– –	– –		– –	– –	– –	– –
20	A S B, g, c w	100 110	120 5	S S	+ +	+ – + +	– – – –	– –		– – – –	– –	– –	– –
21	A S B, c, e				+ – – –	– – – –	– –	– –		– –	– –	– –	– – †
22	*B licheniformis*, c, l	100	4	K	+ +	– – – –	– –	– –		– –	– –	– –	– –
23	*B subtilis*, p, l				+ +	– – – –	– –	– –		– –	– –	– –	– –
24	A S B, p, l	121	30	K	+ +	+ +	– – – –	– –		– – – –	– –	– –	– –
25	*B licheniformis*, g, e				+ +	– – + +	– – – –	– –		– – – –	– –	– –	– –

A S B, unidentified aerobic spore-bearing organism
Object c, cloth g gauze or lint p, paper s, string or thread
Pack c.w, cotton wool e, envelope l, loose t, tube
S survived. K, killed SK, some survivors +, survived. –, killed.
Each + or – represents one replicate test.

* Cultured in cooked-meat medium with subculture to blood-agar, aerobically and anaerobically, as specified by sender
† Few samples received, some tests made on half-portions only

at high temperatures and too narrow at low ones, also it does not discriminate between dry and moist heat If, however, it is used intelligently, at temperatures of 110°C or above, it probably provides the best routine test now current The findings of recent investigators seem to confirm this opinion (Howie and Timbury 1956, Scott 1957, Alder and Gillespie 1957) Although the type-II tube probably provides an adequate safety margin, the use of a lower standard for gloves than for dressings seems hard to justify, especially in view of Perkins (1956) insistence that gloves can be sterilised at 121 C for fifteen to twenty minutes without damage

It may seem revolutionary to advocate the use of chemical rather than bacteriological methods for the routine testing of hospital sterilisers A parallel is, however, provided in the testing of milk for adequate pasteurisation This is now no longer done by bacteriological counts but by purely chemical estimates of the phosphatase surviving the heat treatment

Summary

From a review of the literature, the resistance of certain spore-bearing pathogens to moist heat is compared with the resistance of commonly used test organisms

The resistance to moist heat of twenty-five samples of spore papers currently used for testing hospital sterilisers was determined None was found to be satisfactory

Few, if any, mesophils are suitable for making test preparations, and thermophils should only be used when adequately controlled and for special purposes

For routine tests a chemical indicator is the most useful, and the properties of the ideal chemical indicator are discussed

I am indebted to Prof E T C Spooner, Prof J W Howie, and Dr S T Cowan for advice, to Dr G S Wilson for circulating my request for spore preparations, and to the pathologists who responded to that request

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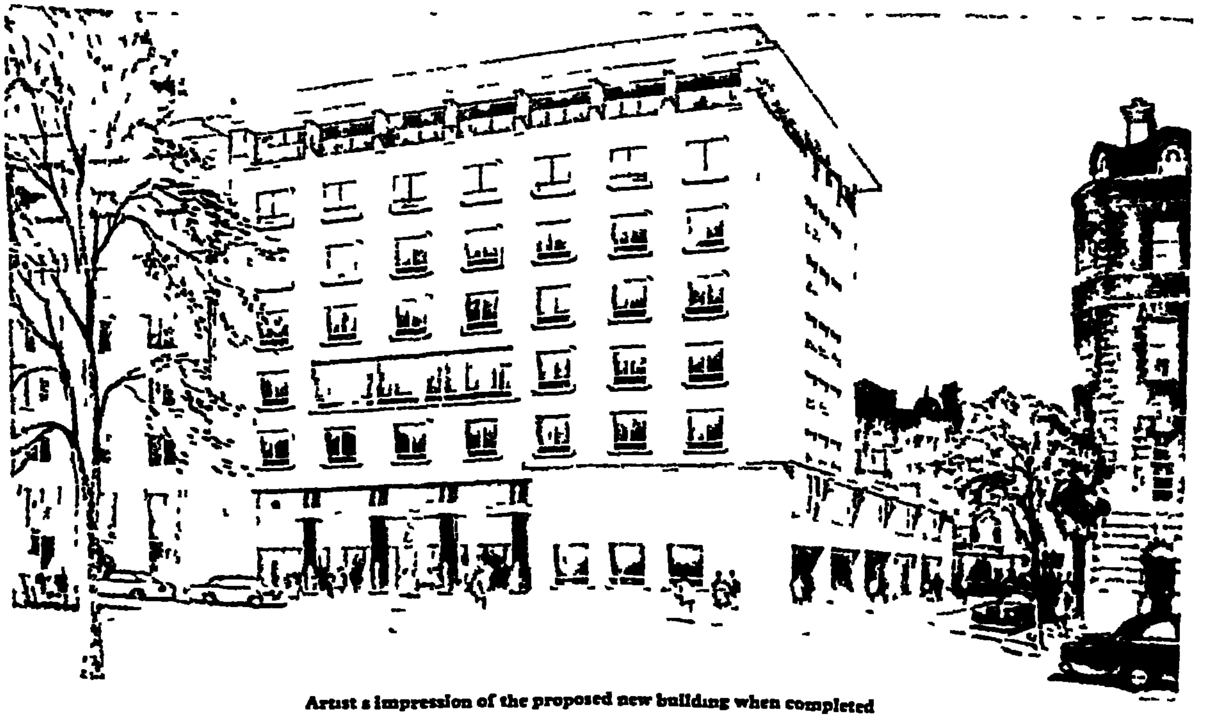
COLLEGE OF GENERAL PRACTITIONERS

PERMISSION has been granted by the London County Council for the new headquarters of the College of General Practitioners to be built alongside the Royal College of Surgeons in Lincoln's Inn Fields

The new building—a gift from an anonymous donor—will contain a conference hall, lecture-theatre, library, museum, council chamber, committee rooms, and restaurant An important feature will be the equipment and premises demonstration rooms, where apparatus used by family doctors throughout the Commonwealth will be displayed, together with models and drawings of different types of premises Other parts of the building will be allocated to undergraduate and postgraduate education, the college's journal, and its research headquarters which will include a records unit and a statistical department, the latter may be of value also to the Imperial Cancer Research Laboratories nearby In addition to books, other publications, and archives, the library will preserve films and sound recordings of interest to general practitioners There is to be an underground garage

The architects are Trehearne & Norman, Preston & Partners The consulting architect is Sir Edward Maufe, R.A



Artist s impression of the proposed new building when completed

The Widdicombe File

XLII—THE LIFE FOR ME

DEAR UNCLE TOM,

You may have wondered what has become of your loving Nephew since our little skirmish of a year ago about those Clinics (Do you know, some M Os H *still* don't believe that G P s exist?) Well, it is the purpose of this epistle to enlighten you

On climbing the barriers round Our Noble Royal College, I looked about me where next? My orthodox medical colleagues I observed having coronaries the year or so after finally achieving Consultant Status in their 40s—those, that is, that hadn't taken up farming or gone to Zanzibar It seems to me, too, that in the popular specialties it is so jolly tough near the top that anyone deviating significantly from the mean is likely to be at a fatal disadvantage To be considered for a consultant job you've got to have won the right letters, done the right jobs, known the right people, said the right things, cultivated the right type of double-breasted-suit-personality and preferably been born to the right Father This produces safe and competent men, doubtless, who won't cause a Regional Board any bother, but it's no good at all for chaps (such as myself) who get a morbid compulsion from time to time to beat the pants off some aspect of contemporary medical life The enucleation of Angry Young Doctors at registrar level or below may have, one fears, an ossifying effect on the upper reaches of our profession in time to come One wonders who will take the place of those distinguished and notorious iconoclasts (such as yourself) who have made medicine what it is? No, the humiliating obeisance of the average senior registrar to his boss is not for your Nephew Richard

Then General Practice perhaps? Holy work without doubt a good G P is worth a couple of dozen average consultants, but I want to grow up with my kids, and anyway even for a bright young man the future is anything but secure On Public Health you know my views already! Radiology? Well, I like people, and I didn't picture myself spending the next 35 years seeing them through a glass darkly Skins are quite pretty and you can zip through an afternoon's outpatients like a fire-engine down a crowded street, but nowadays with hydrocortisone ointment we can all be Dermatologists Neurologists seem a hybrid race, their little academic domain is splitting three ways between the Psychiatrists, the Neurosurgeons, and, in the Provinces, the General Physicians Psychiatry is, in some ways, every bit as empirical as skins, but at least it tries to get to the bottom of things, not only in its own but in *everyone else's* field too, and there was the promise of interest and oddity Also and furthermore, as one of my erstwhile Bosses pointed out "What, going to be a trick-cyclist? Be a Consultant in six months won't you?" And another "If you don't like it you can always get out and pretend you only went in so as to be able to treat the Whole Man" But I've been at it a year now, Dear Uncle, and there is no doubt that this is the Cobbleigh Career

Let me give you my worm's-eye impressions of this very happy time—hastily apologising first for my rude remarks about other callings, set out above, which are just my feelings and not meant to be critical

It's a perplexing life this Not in general medicine would you find three world-famous specialists round one bed coming to three quite different diagnoses and proposing to manage the case in three totally divergent ways At least, not very often

I fell first among the phenomenologists—the Right Wing perhaps—who regarded the Unconscious as an unproven illusion and itemised every possible feature of the patient and his family even unto the third generation They were the people who, according to a traditional aphorism, had the Question to every Answer The approach was as somatic as the smallest print would allow, and long was our reading of The Literature Research was undoubtedly uppermost in the mind of many, but our patients were not submitted to the painful and even dangerous puncturing practices carried on in some places where the quest for Knowledge outstrips ethical reflections The treatment, when applied, was almost always physical, and the patients got better My letters to G P s then ran "Dear Dr Sludge, Thanks for sending this case of depression which we shall probably treat with E C T"

After this I came under the dynamic influence of, as it were, the Left Wing—the psychotherapists Things suddenly began to mean something, and I started reading Freud *Then not only did my patients mean things*, but my wife and kids too, and my horizons became blurred with a pseudosexual mist which made everything *something* I made enthusiastic interpretations to my patients (who usually got well just the same), and even thought vaguely of having an analysis My letters now ran "Dear Dr Sludge, Thank you indeed for sending this fascinating man The arrival of a Mother-symbol appears to have reawakened dormant castration-fears with inevitable fixation of the libido narcissistically towards his Ego-ideal We shall cathect this with extended psychotherapy" But as some of my early successes returned as ill as ever, and my new outlook on life was obviously going to drive my wife to drink or to analysis, enthusiasm waned Nevertheless, although I haven't gone the whole analytic hog, you can take it from me, *Uncle, that old Sigmund knew a thing or two* You don't need to prove his theories "on the couch" they shout at you from every page of the case-notes

But in this confusing subject—where each authority speaks with a different voice and only controversy seems real, where the mind stretches ahead, a great unknown uncharted expanse—*there is to me one great ray of hope*, one island to which I can lash my storm-tossed barque of credulity yes, E C T The first case of melancholia I ever treated, devastatingly depressed, recovered as from the dead with a couple of E C T the age of miracles is not past, and as one after another has found new life and happiness via the magic shock, I have pondered on what lies round the corner, say, for schizophrenia? But apart from E C T there's quite a lot we can do looking through the records of my first 33 cases admitted to the acute wards, 27 have recovered completely, or enough to return to normal life, 4 discharged themselves within a week, untreated, 1 went home I S Q , and only 2 were moved to chronic wards 14 were given E C T at some stage *I don't claim anything whatever from these figures except* to show that this isn't such a depressing dead end as some may think, for anyone who likes to see people getting better

When you get in, too, you find it's a bigger field than you thought for example there's the forensic side, social psychiatry, education, and some chaps have even got going on politics It may be a grandiose delusion, but it seems inescapable to me that, as new knowledge is gained, psychiatric and psychological influence will become very widespread and important indeed

Already, it's a stimulating line, and often very rewarding in many ways I don't think the divisions are nearly as deep as the clash of ambitions and personalities often makes them seem, and I believe that before long you will come to accept a surprising incursion of psychiatric activity around diseases you still regard as "organic" Much of it certainly sounds very funny to somatically tuned ears, but at least we are trying (see how that "we" keeps slipping out) to push understanding one stage further back After all, what do you *really* know about the causes of essential hypertension and ulcerative colitis? The Physicians and the Psychiatrists are peering at each other across the Hypothalamus, before long they will be shaking hands there

I'm afraid it still seems to be *de rigueur* round the General Hospitals to make light of our contributions and to look upon us as a therapeutic last hope if not indeed as subjects for uninhibited mirth Too many of our patients seem to be sent only when every ketosteroid has been checked and re-checked, radio-opaque material inserted into every conceivable tissue, and almost every expendable organ excised These words come more from sorrow than anger, and I must add my whisper to the plea for a bit more undergraduate instruction I reckon it's the *general* men that matter most in teaching hospitals, and those with a real appreciation of psychological factors are still too rare.

I remember a long time ago, before I joined this fraternity, I taunted an elderly psychiatrist with the unworthy remark that in his field he understood little and could do less "May be," he admitted graciously, "but I think we do about as much good as anyone else" He was very right.

With all good wishes,
Your affectionate nephew,
RICHARD COBBLEIGH

Medical Education

TEACHING IN NON-TEACHING HOSPITALS

R E SMITH
M.A., M B Cantab, F.R.C.P
PHYSICIAN TO THE COVENTRY GROUP OF HOSPITALS

WHEN he leaves a teaching hospital to join the consultant staff of a "non-teaching hospital", the senior registrar may think that his teaching days are over and that he will lose the stimulus of regular contact with students In his new environment, however, he will soon discover that he is a perpetual teacher, or at least may be if he so desires

POSTGRADUATES

Advances in medicine have brought more work for residents, and the physician's or surgeon's complement has been increased to a houseman and a registrar (or senior house-officer) instead of a houseman only (or perhaps nobody) In small hospitals registrars still do not abound, but commonly the consultant will have both a recently qualified house-officer, who is seeing a new and often more representative type of hospital practice, and a registrar who is aspiring to a higher qualification or diploma While he can learn much from these pupils, they can learn more from his years of experience Every round can be a teaching round, without the boredom of explaining elementary facts to the undergraduate It is a mutual-benefit society where all contribute—including the ward sister or staff-nurse

In the hospital group in which I work, there are two other types of postgraduate activity One is a monthly visit from the university professor, the other an after-tea demonstration of interesting cases organised by a senior resident

The professor sees three or four cases, usually with unusual and perhaps perplexing symptoms, or maybe something of which the consultant dreams, such as hypercholesterolæmia or chronic meningococcal septicæmia. "Debunking" is his prerogative, but some of the patients, to use his own words, "develop interesting complications" not hitherto reported in the disease he has diagnosed These rounds are really enjoyed by the local physicians, who have to work hard to present their cases The pleasure has been enhanced by the professor's being joined on occasions by other notables, such as the president of the Royal College of Physicians or of the Association of Physicians, the regius professor of physic at Cambridge, and a visiting professor from Boston With such talent, it is usual to produce at least one patient with a disease of the system on which the visitor is an expert

The after-tea demonstration always produces some surprises and always evokes a good discussion Cases are demonstrated by the residents or the consultant and postmortem specimens and cases shown a second time often afford salutary discipline

I have said enough, perhaps, to show that postgraduate education is a major activity of "non-teaching" hospitals

THE FAMILY DOCTOR

In the past four years, we have had three refresher courses for general practitioners We had little idea what the demand would be, but applications for each succeeding course have increased

It has been said that a clinical lecture should be exhilarating and exhausting So is a clinical demonstration A recent course showed that only the seasoned lecturer can go on for more than an hour Our courses have always been eleven sessions of 2½ hours with a break of 15–20 minutes for tea in the afternoon, or coffee in the morning About twenty subjects must be selected. One or two occupy the whole morning or afternoon. With the help of our patients an expert in gastro-enterology or in chest surgery can interest his audience for the whole session, but the local specialists are content with an hour, and if they deal with two aspects of their branch of medicine, they prefer two separate days All aspects of medicine and surgery are considered but the emphasis is on medical problems

It is sine-qua-non that all is designed to help the general practitioner in his daily work. Recent advances such as the sulphonamide treatment of diabetics, the use of steroids in the management of hæmolytic disease, and the great advances in the treatment of neonatal deformities are examples of the subjects that the general practitioner likes Certainly one does not want to be too abstruse and too scientific, but it is a worse mistake to suppose that one should talk down to general practitioners

There is much to be learnt about organisation and method

One of the earliest experiments in postgraduate education was undertaken in Edinburgh in 1953, when the course was held on Sunday mornings Questionnaires at the end suggested that this was the most convenient day and our experience is the same We have had one course in which people were invited fortnightly on Sunday morning and fortnightly on Thursday afternoons, and the Sunday attendance averaged 24 against 18 on Thursdays We have tried to have courses in the middle of the week because most doctors take their half-days then, and it is surprising to me that general practitioners are so often willing to sacrifice their leisure to attend them

TEACHING NURSES

The General Nursing Council holds that lectures on clinical subjects wherever possible be given by doctors, and this is almost always done Nurses are taught anatomy and physiology on a theoretical basis because practical classes in medical subjects cannot be arranged To add to the nurse's difficulties, she has often had no basic training in chemistry, physics, or perhaps in biology Yet despite all handicaps, nurses are eager to learn the principles of medicine and surgery and of the specialties

Because of these limitations, those who teach nurses should take care to make themselves clear, concise, and factual Nurses appreciate clinical demonstrations, and some patients are very willing to return thanks to the hospital by coming annually A mitral stenotic, formerly bedridden, fibrillating, and scattering emboli, will tell nurses how after her operation she returned to work, and a patient with Addison's disease will relate her improvement after being given salt and deoxycortone but will rise to say that, after a week with cortisone, she told her daily woman that she would not require her any more Blood-films, temperature charts, and photographs all help

Anyone who thinks that he can just walk into a nurses' lecture-room and speak for an hour should do two things Firstly, he should take note of his audience at the end, when he does take preliminary trouble and when he does not, and compare the alertness with the yawns Secondly, he should correct nurses' examination papers He will then find that nurses who have been taught well have a very high standard, and let me say that this reflects much more credit on the sister-tutors than on the doctors giving lectures

Many people think that we are training nurses now on far too scientific a basis I do not belong to that school, I cannot see how modern medicine and modern nursing can be carried on unless the people practising it understand the reasons Furthermore, if we are to make nurses good observers, they must know what to look for In other words, the medical and nursing professions are allies, each with responsibilities, and I, for one, think that the time will come when we shall organise postgraduate training for nurses, which to my mind is grossly neglected

I cannot understand why in one branch of nursing—midwifery—there should be a special course and a special diploma, which carries great weight when nurses are applying for senior posts, whereas in general medicine or general surgery there is no such diploma for the postgraduate nurse The time is probably not far distant when children will have the benefit of being nursed by those who have had a special training in pædiatrics If ever a scheme for postgraduate education in general medicine and surgery evolves, it will probably be started by some enlightened matron, who realises that what is sauce for the midwife is sauce for all other staff nurses and embryonic sisters

MEDICAL AUXILIARIES

Besides hospitals connected with a university, there are a few which have been made responsible for the students of professions ancillary to medicine In our group, we have schools for orthoptists and for radiographers The training of radiographers, much of it practical, lasts about $2^1/_2$ years The physicist gives half the lectures (which number about 100) and the consultants the other half

UNDERGRADUATE STUDENTS

From what has been said, it is evident that in the non-teaching hospital one teaches almost every type of student except undergraduates, and even this exception is a little doubtful For several years we have had applications from students at teaching hospitals, who have been advised to go and get experience elsewhere In hospitals where the houseman takes a holiday doing his 6 months' residence, a student working under supervision, may temporarily take his place, but for most of his 2–3 months' stay he is acting as a clinical clerk—taking histories, making examinations, taking blood, and, under his senior's eye, doing perhaps his first lumbar puncture or pleural tap

Sometimes these students go to a particular hospital because it is near their home But then they may tell their friends about it, and so the tradition grows up that it is a good place to go to

In our group, the only consultant who has students sent him from the university is the obstetrician and gynæcologist, who is recognised as a clinical tutor Two students go to him regularly, and they get infinitely more experience than they would in their teaching hospital To come to us is much simpler and cheaper for them than going to faraway Dublin, as was formerly done by so many students from the London hospitals, and, just as postgraduate training of nurses in midwifery sets an example for postgraduate training of nurses in other medical specialties, so I think that this training of gynæcological students points the way to a better training of students in other branches of medicine—particularly in general medicine, which will probably always remain the basis of medical education

In the teaching hospitals, in a clinical course of about 3 years, a student spends only 6 months in general medical clerking, and sometimes with only one group of physicians The objection to sending him out into neighbouring hospitals within the region is that he misses lectures, which are often designed to complete his formal training But on balance, he would probably learn more in 3 months' clerking to a general physician in a large peripheral hospital where the clinical material is abundant and interesting, besides giving a better idea of the commoner diseases Moreover, a steadily increasing proportion of physicians in these hospitals have served a teaching apprenticeship as registrars in teaching hospitals

MEDICAL SOCIETIES

Medical societies are on the increase, and the temptation is to join too many To be a member of the local medical society is a privilege and responsibility It brings one in contact with one's fellows in the same town, but the consultant usually contributes more than the general practitioner and is often asked to go to other towns Then there are the regional societies, and my experience of these is of growing prosperity The East Midlands Association of Physicians is the oldest and carries on at a steady tempo The West Midlands Association of Physicians is only 7 years old and often has to refuse communications

Although the audience might resent the suggestion that it is being taught, and the speaker that he is teaching, in fact that is what is happening, and most people come away saying that they have learnt much Furthermore, the man who has to present a paper at any of these meetings learns much himself

TEACHING ONESELF

There are so many ways of teaching onself that it is difficult to know what to single out Regular reading of the journals is essential, although very often the summary of an article suffices to tell one if there is anything new in it Attendance at medical meetings serves two purposes —the advancement of knowledge and the promotion of friendship, and certainly it is much easier to read articles if one knows the authors of them Perhaps the consultant learns most by pursuing one particular subject, as he has to do if he is writing a paper Some regional boards are liberal in giving study leave, which is another way of saying that they know that the consultant is still a student Travelling clubs, visits abroad, visits from others of one's own standing, or perhaps visits from professors—all help to widen one's interests and advance one's knowledge Some people will get most from preparing a paper, others from watching or listening But all will notice that in their teaching they introduce things that they have learnt elsewhere, and they will find increasingly that, as J H Sheldon said, work in a non-teaching hospital can be fully satisfying

Public Health

THE WORK OF W H O

THE record[1] of the activities of the World Health Organisation in 1956 gives a vivid picture of the remarkable scope of the Organisation's work and the magnificent results that are being achieved

CONTROL OF INFECTIOUS DISEASES

Mass campaigns against *leprosy* with sulphone drugs have reduced the need for long and expensive hospital treatment and lifelong segregation in leprosaria Much attention is being paid to finding an effective long-acting drug In Nigeria treatment is based on temporary segregation and outpatient supervision by both fixed and mobile units responsible for the oral administration of the drug, whereas in French territories mass treatment consists of a fortnightly injection of an oily suspension of dapsone—a scheme easily adaptable to rural areas Of the 150,000 leprosy patients in French Equatorial Africa, 100,000 are now under regular treatment, and a similar project has been initiated with the Government of French West Africa, where the number of patients is estimated to be 500,000 Case-finding by examination of contacts and health education of the public to dispel centuries-old fear follow the lines of campaigns against tuberculosis and treponematosis

Spectacular results have been achieved against the disfiguring *yaws* By the end of 1956 more than 55 million people had been examined and 16 million treated with long-acting penicillin in W H O /UNICEF-assisted campaigns Serious reactions to procainebenzylpenicillin in oil with aluminium monostearate have been reported from urban areas and have directed research towards new preparations which may be free from side-effects, but it is interesting to learn that little evidence of reactions has come from underdeveloped rural areas, children not previously exposed to antibiotics being particularly free from trouble The splendid results after only one injection are a little-known triumph of penicillin and a tribute to those in UNICEF and W H.O who have organised such rewarding campaigns against treponematosis Some thirty national and other laboratories all over the world are now helping in the search for a practicable method of serum diagnosis in the treponematoses

Mass treatment of *trachoma* has for long been difficult because of the need for repeated daily application of antibiotics to the eye and the strict control of personal and domestic hygiene In North Africa much of the treatment is now left to teachers and schoolchildren who have been instructed in the common rules of cleanliness and in the application of antibiotic ointment to the eyes of their schoolmates The W H O report has impressive photographs to illustrate this promising scheme.

The attack on *malaria* has continued over vast areas of the globe, and the report's comprehensive maps show the extent of eradication already achieved and where campaigns are still in progress A new project has begun in Mexico, where it is estimated that there are 2 million cases a year, and where districts potentially the richest in agriculture, livestock, fisheries, petroleum, and sulphur mining are the worst affected UNICEF is sending supplies and equipment worth nearly \$8½ million, the Mexican Government is investing more than \$12 million, and W H O has awarded fellowships to train more than 1300 specialists Wherever possible W H O malaria teams are now testing the susceptibility of local vectors to different insecticides Where anopheles has become resistant to dicophane (D D T) it can often still be controlled by gammexane (B H C), but some strains are resistant to both Another method of malaria control is the distribution for human consumption of table salt containing pyrimethamine or chloroquine The first results in volunteers inoculated with malaria have been encouraging An interesting sideline of malaria control is reported from South-East Asia spraying, particularly "patch-dusting", seems to combat the rat flea, and has thus diminished the incidence of *plague*

Smallpox still persists in some areas where vaccination programmes have been carried out Rapid loss of potency of the lymph under tropical conditions has been the principal cause of failure, even where dried vaccines were used During 1956 a freeze-dried vaccine became available with which, in the Latin Americas, eradication programmes were started *Pertussis* vaccine became the first bacterial vaccine to be internationally standardised, "a unique achievement in the history of vaccine control"

An estimated 40,000 children in Syria were affected with *favus* This fungus infection of the scalp is a serious social and medical problem, particularly because it interferes with education Under a new project started in 1956 30,000 children were examined and 7000 treated

TUBERCULOSIS

In the report's comments on the several B C G campaigns which were completed, it is frankly admitted that in some mass campaigns vaccines were of poor quality and techniques and organisation defective A new plan for anti-tuberculosis drug trial projects has been put into operation, and in 1956 one such project began in Madras in association with the British and Indian Medical Research Councils (The preventive value of *p*-aminosalicylic acid and isoniazid was demonstrated in the W H O /UNICEF Thailand scheme[2]) From the Madras project, which is conducted by clinical and laboratory experts from this country, much valuable information on simplification of treatment schemes and on resistance and virulence of the tubercle bacillus under oral chemotherapy is expected during the five years for which this project is planned

SANITATION

An environmental sanitation project, which may be of world-wide importance, was organised in Japan In Asian countries traditional methods of collection, disposal, and utilisation of organic wastes have always been unsatisfactory It has been estimated, the report says, that the health of over 500 million persons is affected by undesirable sanitation practices In Japan the use of human excrement as fertiliser has been responsible for the transmission of many of the endemic intestinal diseases In Kobe a pilot plant for aerobic composting of both urban refuse and night soil has been put into operation to find out whether these materials can be economically processed to produce a useful and acceptable end-product This method is practical and economical, and the product is free from pathogens The Japanese Ministry of Health has allocated $1 million to subsidise similar plants

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[1] Annual Report for 1956 of the Director-General of W H O Official Records of the World Health Organisation no 75 March 1957 Obtainable from H.M Stationery Office, P O Box 569 London S E.1 10s

[2] Benatt, A J *Lancet*, 1956, i, 736

REFUGEES FROM PALESTINE

In 1956, 44% of the 900,000 Palestine refugees lived in camps in the Lebanon, Syria, Jordan, and the Gaza area, and the rest in towns and villages During 1956 over $5½ million was spent on health services for these refugees (chiefly through the agency of UNRWA) Besides 19 international health workers, 3350 were recruited from among the refugees themselves, to whom a number of training scholarships were given 2200 hospital beds and 90 outpatient departments were in use None of the six quarantinable diseases occurred during the year, probably the result of inoculations and the provision of a safe water-supply The number of cases of clinical malaria dropped to nearly half that recorded in 1955 Tuberculosis wards were opened and a new 150-bed wing was prepared in the Lebanon for tuberculous refugees Supplementary feeding schemes for pregnant women were introduced, and infant-feeding, milk-centre, and school-milk programmes were expanded An extra $100,000 were approved for the care and training of blind, deaf, and crippled children

INFORMATION SERVICE

W H O 's information service includes the publication of a book for secondary schools, *Mankind against the Killers*, of which a popular edition has been issued, widespread distribution of the W H O News Letters, and a revised edition of the information folder about W H O and what it does There have been radio talks on the effect of radiation on human heredity and other feature programmes on the peaceful use of atomic energy A film on alcoholism, *To Your Health*, received the Edinburgh award

Infectious Diseases in England and Wales

Disease	Week ended January			
	4	11	18	25*
Diphtheria	6	7	2	1
Dysentery	546	574	671	829
Encephalitis				
Infective	2	3	5	2
Post-infectious	—	5	3	1
Food poisoning	137	139	159	127
Measles, excluding rubella	3523	2888	2443	2338
Meningococcal infection	33	34	23	39
Ophthalmia neonatorum	37	22	20	25
Paratyphoid fever	8	7	7	1
Pneumonia, primary or influenzal	1349	1294	1059	917
Poliomyelitis				
Paralytic	28	28	22	18
Non-paralytic	8	8	9	6
Puerperal pyrexia	209	235	196	204
Scarlet fever	652	501	679	821
Smallpox	—	—	—	—
Tuberculosis				
Respiratory	482	566	606	541
Meninges and C N S	5	5	11	6
Other	49	45	48	52
Typhoid fever	1	2	2	2
Whooping-cough	449	460	444	569

* Not including late returns

Medicine and the Law

Evidence of Feeblemindedness

IN October, 1952, a young man aged 19, an agricultural worker, pleaded guilty to stealing two and a half pints of milk, for which he was placed on probation for one year In January, 1953, he was brought before justices for breach of the probation order and was remanded to Canterbury prison for a medical report On Feb 2, 1953, the justices, being satisfied on medical evidence that he was a defective within the meaning of the Mental Deficiency Acts, 1913 to 1938 (as amended), being a feebleminded person, made a detention order under section 8 of the Act of 1913

It appeared from the affidavits that no written reports were before the justices but that the prison doctor who had examined the young man wrote to the justices' clerk indicating the results of that examination and gave oral evidence to the same effect as his letter In that letter the doctor said that the young man's backwardness "is clearly the result of mental defectiveness and his reasoning and judgment are grossly impaired I am of the opinion that he is a feebleminded person within the meaning of the Mental Deficiency Acts and that he requires care and treatment"

The young man applied to the Divisional Court for a writ of *habeas corpus* directed to the medical superintendent of Moss Side Hospital, Maghull (where he had been transferred by order of the Board of Control) alleging that he was not and never had been a mental defective and that the detention order had been made without jurisdiction

The grounds of the application (among others) were that under section 1(2) of the Act of 1913 (as amended) mental defectiveness for the purpose of section 1 meant a condition of arrested or incomplete development of mind existing before the age of 18 years and that there was no evidence before the justices that he had suffered from such a condition before he was 18, or that the defectiveness was so pronounced that he required care, supervision, and control for his own protection or that of others [see section 1(1) (*c*)], and therefore it was not proved that he was a defective within the meaning of the Act

Counsel argued that it did not seem that the young man's condition before he was 18 had ever been considered and that it was not sufficient for a doctor to come to court and state his conclusion that a person was a feebleminded person within the Act without saying that he had inferred that the condition had existed before the age of 18 or how he had arrived at his conclusion

The LORD CHIEF JUSTICE, giving judgment, said that the justices, hearing that the young man was living in a hut on a farm and was then 19, remanded him for a medical report, obviously they had done so because they wanted to know if he was a mental defective or not and it was to be observed that they had had the opportunity of seeing him The prison doctor—a man well acquainted with the Mental Deficiency Acts—had said that he was a feebleminded person within the Acts That was only a compendious way of saying that he had examined the young man and had come to the conclusion that the provisions of the Act applied to him The court was asked to say that there was no evidence on which the justices could have made the order for detention, but their Lordships thought that on the evidence it was open to the justices to make the order On an application for a writ of *habeas corpus* the court had to see whether the detention was lawful, the young man was detained under a lawful order but if it could have been shown that that order was made without evidence the court could go behind the order It was plain, however, that there was evidence on which the order could be made, and the application must be dismissed

Mr Justice HILBERY and Mr Justice SALMON agreed

IN RE SAGE *Queen's Bench Division (Divisional Court)* Lord Goddard, *C J*, Hilbery and Salmon, *J J* Jan 27, 1958 Peter Pain (Walter Stein & Grover), Rodger Winn (solicitor, Ministry of Health)

J F LAMB
Barrister-at-law

In England Now

A Running Commentary by Peripatetic Correspondents

I HAVE been waging war on sleeping tablets Every patient who asks for them, or who obviously hopes for them, is submitted to a series of questions The results of my investigation are startling In my series of about fifty patients with insomnia

> Only three patients went to bed later than 10.30 P.M Most went to bed at 9 30 P.M or earlier One went to bed at 5 P.M
>
> Only one patient spent less than 9 hours in bed each night The average time in bed was $10^1/_2$ hours and the maximum was 15 hours
>
> All the patients thought their health would suffer if they did not sleep for at least 8 hours per night.

Insomnia is often said to be a symptom of anxiety or depression, but my investigation suggests that it is more commonly a symptom of boredom or ignorance The ignorant are sometimes cured by a simple statement that the human need for sleep varies and may be as little as 4–6 hours The bored are more difficult "What on earth would I do with myself, doctor, if I stayed up later?" I don't know the answer to this, but I do not believe it is sleeping tablets

• • •

After octogenarian Uncle Fred was moved from Bromley-by-Bow to the Surrey Hills, he complained not of the quiet but of the everlasting banging and hammering which kept him restless through the day and often woke him in the early hours "Soon fix you up, Uncle Fred," I said, and turning to the out-all-day nieces I added "Tinnitus aggravated by senile arteriosclerosis See that he takes one pill every four or five hours Chlorpromazine often acts well—never mind the name. No—not constipating"

The following week, I looked in to find him still fretting about the ill-mannered hammering A few minutes later, while taking his pulse, I heard it myself Staccato, insistent, loud followed by a rather dirty sort of laugh "Well, if the people next door ignore your request to be more reasonable, it might constitute a nuisance under one of the by-laws," I conjectured "We might enforce it I'll find out for you"

It was almost dark and there was a slight drizzle I stepped down from the porch into the car and, switching on the headlamps, looked straight into the dazzled yet sharp, unwinking, libertine eyes of the violator He gave the impression of tremendous latent energy—his carmined head thrown back, a ponderous midriff, and short powerful legs—clad in rich dark green, he embraced the nearest tree-stump "Never seen a woodpecker that size," I mumbled to the nieces, feeling rather foolish, and, putting my foot down, both man and bird accelerated tangentially into the outer darkness

I was still puzzled by the queer laugh, but, while my soup was getting cold, I read in *Britain's Birds and Their Nests* that not only is the hysterical cry popularly supposed to foretell rain (hence the local name "rain-bird"), but the name "yaffle" or "yaffer" refers to his cry "When disturbed there will often break rudely upon our ears a burst of demoniac laughter, 'Heu, heu, heu, heu, heu'—a something between a laugh and a neigh"

• • •

Our fogs may be worse, our respirators better, but are our advertisements as well written as this example from *Wolferstar's Guide to Midhurst*, 1884, for Bourne and Taylor's Anti-Fog Respirators and Life Preservers

> It is an alarming fact that during the prevalence of the extraordinary fogs which made the winter of 1879–80 notorious, the lives of many hundreds of our fellow-creatures were needlessly sacrificed, and most of those who fell victims might have been alive now if they had taken the precaution to wear a Respirator
>
> The sale of these instruments during the past few years has been steadily increasing and we take to ourselves the credit for having introduced some of the neatest and least unsightly patterns ever produced and by these means have broken down the barrier to their universal use
>
> No doubt a prejudice has long existed against the use of these Life-Preservers, and not without reason, for some are as hideous as it is possible to make them, and instead of being a source of comfort they make the face hot and produce a feeling akin to suffocation
>
> In the year 1863 Mr Johnson made the scientific manufacture of these instruments his special study and after much care and many experiments succeeded in producing a Respirator of real practical worth in such a variety of shapes etc. that we now guarantee a perfect success to the most fastidious There are now 26 patterns and in various colours, some almost invisible

No 1	The Respirator for the million	1/-
	Silver-plated wire	2/6
	Gold-plated wire	6,-

* * *

Methods of retirement differ in different professions The successful barrister may hope that in his later years he will be a judge, with a steady income for steady work. The Church has no satisfactory alternative to retirement, though there are ex-bishops, Lord Davidson of Lambeth is the only archbishop who has retired Schoolmasters in public schools, usually regarded as a conservative body, set us an example of progress The modern practice of giving the best man a house for fifteen years when he is in his late 30s means that his chances to do his best work come when he is in his prime instead of after it The former headmaster of Malvern, who on resignation joined the staff at Winchester as an ordinary master, may have set a new and sensible fashion.

In our profession the retiring age for consultants is fixed, or almost fixed, at 65 General practitioners can go on for ever, though of course they can usually limit their lists by not taking new patients or by taking a partner, but the consultant is not so lucky, and an "all or none" law may enforce itself Even so, the really busy consultant should seek means of cutting his commitments Those final five years may be telling, unless he sheds such extras as physician to the nurses, lecturer (and the General Nursing Council want more than ever), and, above all, sitting on committees These may be "the drowsy syrup of democracy" for some, but to the John Hunters of the profession they are aggravating time-wasters

• • •

Twelve weeks ago we operated on a lady aged 103 for a fractured femoral neck She has an excellent result with full painless movement and is walking well The credit, of course, is due to her extraordinary vitality Her sight and hearing are very good—no glasses, no hearing-aid I was introduced to her "girls"—one 82, the other 76 She also has a "boy" somewhat over 70 who in a third marriage has a child aged 3

• • •

A rather dull outpatient clinic was redeemed this morning by Mrs Smith She was a healthy-looking young woman who had her first baby eight weeks ago A few days after a normal delivery she complained of an agonising pain which began in the fingers of each hand and spread up to the shoulders The pain was present night and day and was unaffected by the analgesics her doctor had prescribed As she went over to the examination couch, my house-physician, a recent father, whispered to me "She probably doesn't like the nappies" I deprecated this glib and somewhat frivolous diagnosis

Careful examination showed no abnormality in Mrs Smith's central nervous system and I asked her if she were particularly busy at home. "Yes," she replied, "I am very busy, but things should be easier now, I am going to put my husband on to the nappies"

• • •

News from School—Outside my window a Spanish maid is singing a folk-tune to ease the burden of her work. Quite well too I must go dish-washing in Spain with a tape-recorder It has stopped now Perhaps she has reached the egg plates Last night a celebrated racing driver, came and told us how to win Le Mans twice running which should be useful information First, take your Jaguar A wild flamenco is rising from the kitchen now, so I cannot vouch for the teaspoons at tea They are giving us more and more things to do once a week—e.g., three-hour French papers I must see whether these will take more time than will exist

Letters to the Editor

INFORMAL ADMISSION OF MENTAL DEFECTIVES

SIR,—I write as the medical officer of a large and, I like to think, progressive hospital for mental defectives, whose policy is to train as many patients as possible to take their place in the community as soon as their rehabilitation is complete In this post I have often found myself caught in the cross-fire between the forces of the "Civil-Liberty" Guards on the one hand and those of the "Protect-the-Public-at-all-Costs" Brigade on the other The main strength of each force appears to be such that they might appropriately be called the "reds" and the "blues" respectively, with supernumerary strength derived from the less responsible sections of the press, both national and local, vacillating apparently according to the circulation-appeal of either cause at a particular time

It is not surprising, therefore, that I should feel considerable concern at the publication of a Ministry of Health circular recommending the informal admission of mental defectives to mental-deficiency hospitals and at the uncritical enthusiasm with which politicians and press have welcomed this allegedly great advance

The modern concept of mental deficiency is that of social incapacity of such a degree as to render an individual in need of care, supervision, and control for his own protection or for the protection of others Mental illness, on the other hand, in almost all cases, arises in individuals previously able to lead a fully independent existence However, examination of the circular suggests that the Ministry of Health regards the mental defective *as more capable of self-care* than the voluntary patient with mental illness, in that he is to be allowed to leave hospital *immediately* (i e, without the seventy-two hours' notice at present required of the voluntary patients in a mental hospital) should he not respond to persuasion from the medical officer to remain I visualise "persuasion" becoming the signal for the "reds" to load and for the war-reporters to hasten to the scene On the other hand, let one of these patients wander away from hospital and be involved in injury to a member of the public and the "blues" will attack with full press support

It is true that the more severely handicapped mental defective could be admitted informally, provided that the medical officer of the hospital were given power to detain him for a prescribed period pending provision for alternative care, should this prove necessary, without the risk of allegations of wrongful detention being subsequently levelled However, this seems to offer no advantage over an extension to all grades of mental defectives of the present arrangements under which the parents of these patients may place them under hospital care and retain the right to withdraw them on giving notice, so long as they are able to provide a satisfactory home for them

On the other hand, the admission of the higher-grade patients to mental-deficiency hospitals results from their failure in the outside world, and any successful rehabilitation and training, which is of necessity prolonged in most cases, will be impossible if they are to be allowed to leave hospital whenever they wish It is unrealistic to believe that they will be sufficiently self-critical to appreciate their own shortcomings and the benefits to be derived from further stay in hospital, particularly if they are encouraged in their resolve by the outside influences I have mentioned I believe that for these reasons detention orders will be necessaary in a higher proportion of these cases than the circular would suggest

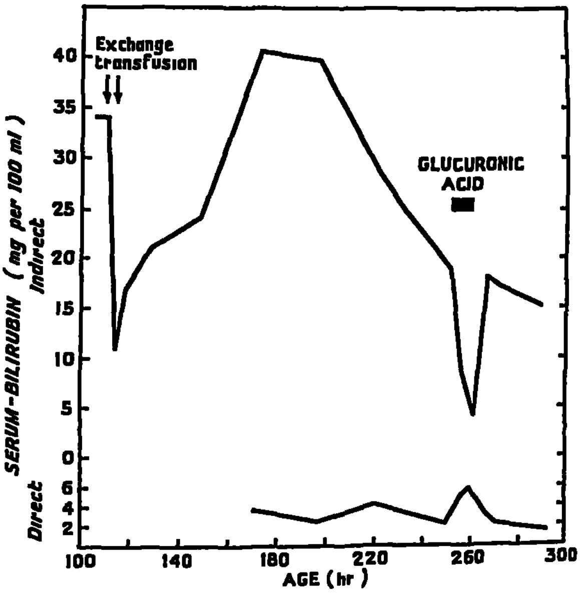
The new recommendation will, I believe, expose the medical officer to even more concentrated cross-fire, while removing the protection previously afforded him by powers designed to safeguard the interests of the patient and the general public

Bristol W A HEATON-WARD

REDUCTION OF INDIRECT BILIRUBINÆMIA IN VIVO

SIR,—Indirect bilirubin is believed to be neurotoxic in high concentration, and current theory attributes the kernicterus associated with hæmolytic disease of the newborn to such injury Kernicterus is also seen in some cases of physiological icterus associated with hyperbilirubinæmia, especially in premature infants Exchange transfusion, now widely practised to treat these conditions, is a cumbersome procedure, not entirely without risk[1]

We have attempted to reduce the indirect bilirubinæmia in such cases by the oral administration of glucuronic acid It was thought that this might favour the conversion of the relatively toxic indirect bilirubin to the less toxic and more readily excreted direct bilirubin, which is known to be a glucuronic-acid conjugate Considerable success has been achieved by this measure In 16 out of 27 cases we have observed a sharp drop in the level of indirect bilirubin, which persisted as long as the oral medication (1 g per hour by mouth) was continued (see figure) In some instances, but not in all, this was associated with a simultaneous but smaller rise in the concentration of direct bilirubin In 11 patients no definite response was obtained 1 of these, a premature infant, was subsequently given intravenous glucuronic acid with a striking response



Change in serum-bilirubin in one patient on glucuronic-acid treatment.

These preliminary observations suggest that oral therapy with glucuronic acid may prove beneficial in the prevention of kernicterus in a considerable proportion of cases and may serve to replace exchange transfusion

STUART DANOFF
CHARLOTTE GRANTZ
AUDREY BOYER
L EMMETT HOLT, JR

Department of Pediatrics,
New York University College
of Medicine

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[1] Walker, W, Mollison, P L. *Lancet*, 1957, i, 1309

THE "LADDER"

SIR,—Your publication (Jan 25) of Lord Moran's letter regarding his evidence before the Royal Commission is timely for many of the profession who read with dismay his remarks as reported in the Press will have been waiting for an explanation

The core of the matter surely lies in the belief that "there is a ladder and that ladder can be maintained" Whether his remarks are "obnoxious" or not is not the main issue The main issue, surely, is that here we are confronted by one who is publicly regarded as a leader of the profession, and whose breadth of vision yet extends no further than to place all the various disciplines of medical practice on the ladder of specialisation which he himself has climbed The simplicity of it is breathtaking

Surely it is a sterile occupation, with a certain lack of humility, to argue which of two quite differently occupied people is of more use to the community, when the services of both are needed Indisputably, the run of family practitioners are not as highly qualified as the run of consultants equally indisputably the run of consultants is not as widely qualified as the run of family practitioners But might not Lord Moran turn his attention—as one hopes the Commission will do—to the problems of encouraging a rising standard of family practice, which remains the core of the Health Service?

Economics is but one instrument for such encouragement. If Lord Moran feels that merit awards "make men keener", and "keep the profession on their toes", he might even consider applying it to family practice He might also weigh the possibilities of equipment grants, of subsidised study leave (financially an impossibility to most G P s at present), of grants for secretarial and administrative help to the G P All these are economic aids which would increase his efficiency greatly, and remove whatever present temptation there is for the G.P to increase his personal income by reducing his practice expenses Such expenditures of State money are absolutely controllable, and accountable for

Nailsea, near Bristol H. J Wright

LONG-TERM TREATMENT WITH ADRENOCORTICAL HORMONES

SIR,—Dr Dudley Hart (Jan 25) rightly urges the importance of increasing the established cortisone dosage to cover surgical operations and all forms of stress This is true not only for those patients whom he and Dr Davis and Dr Popert (Jan 4) describe, to whom cortisone is being administered in pharmacological doses, but also for those patients with Addison's or Simmonds' disease to whom replacement therapy is given in physiological doses Indeed additional replacement therapy is especially important in these patients to compensate for their inability to respond to stress A recent experience has shown how rapidly and severely stress may affect such a patient, if he does not remember to increase his cortisone prophylactically

My patient is a woman, aged 43, who sustained a postpartum pituitary necrosis (Sheehan's syndrome) fifteen years ago She leads an active country life, enjoys playing tennis, and maintains good health on a daily dose of cortisone acetate 37 5 mg and desiccated thyroid gr 2 (120 mg) She drove twelve miles to Norwich on the afternoon of Saturday, Dec 14, to do her Christmas shopping She struggled to find a vacant car park, to walk along the crowded pavements, and enter the hectic shops When she finally struggled home again and had her tea, she developed abdominal pain, vomited, and became comatose I was called to her house, to find her in an addisonian crisis

Estimates have been made in the past of the stress involved in various situations in life The effects, for instance, of participating in the annual Harvard-Yale boat race have been measured in the crews, coxswains, and coaches Patients with Simmonds' disease may not be exposed to the stress of a boat race, but they may find the stress of Saturday afternoon Christmas shopping just as severe.

Bungay, Suffolk. W M Jordan

PARADOXICAL ELECTROCARDIOGRAM IN CORONARY EXERCISE TEST

SIR,—Dr Geoffrey Bourne's account, in your issue of Dec. 28, of a paradoxical electrocardiogram in a coronary exercise test ends with the comment that he has been unable to find any published report of this phenomenon I would respectfully draw Dr Bourne's attention to *Principles of Clinical Electrocardiography* by Dr Mervin J Goldman[1] On page 181 it is shown how the inverted T waves of an established infarction can suddenly become upright as a result of an attack of coronary insufficiency and how, on the following day, the T waves again became inverted as they were in the original pattern of the established infarction

Johannesburg Isaac Freed

THE CHECK-VALVE MECHANISM AND THE MEANING OF EMPHYSEMA

SIR,—I agree with Dr Morris and Dr Widdicombe (Jan 25) that there is little experimental evidence that a widespread check-valve mechanism in the bronchioles is the first step towards the production of emphysema, but the clinical evidence is very strong indeed

It is a commonplace that in asthma inspiration is relatively short and silent, whereas expiration is long, wheezy, and obviously obstructed A careful personal and family history in emphysematous patients will nearly always elicit evidence of gradually increasing breathlessness on effort and winter cough, or of relatives similarly affected

I do not think they are right in saying that overdistension of the air-sacs cannot be uniform because the total distension of the lungs must remain within the limits of a (healthy) person's vital capacity Clinically and radiologically the thoracic distension in asthma would appear to be clearly beyond anything that a healthy man can achieve, however powerful his inspiratory effort may be It was unfortunate that the captions appeared under the wrong illustrations in my paper, though the error would be apparent enough The "normal" chest was my own, for I wanted there to be no mistake about it, and I can assure you, Sir, that my inspiratory effort was maximal, yet the result falls well short of that achieved by the emphysematous patient. If I am right there is no need to assume that some alveoli must be relatively collapsed to allow room for others that are overdistended

Finally, it is a clinical fact that high positive pressures may be found in tension cysts or pneumothorax. The air can come only from the larger air-tubes, and somehow or other it must be pumped from them into the cavity and retained there by valve action. Dayman's experiments, to which I referred, suggest that even in normal breathing there is some check-valve action in the larger air-passages If his opinions can be confirmed, there will be no need to invoke coughing to produce the pressure-drop required to force air into the cavity, though, of course, with a cough the effect would be much greater We have here an exact analogy with a bicycle pump—one valve in the pump and another in the tyre—and a mechanism that can equally well explain a high pressure in a single cavity or a constant, gentle overdistension of all the alveoli in the lungs Release the valve in the tyre, or give an injection of adrenaline, and pump or cough as you may the tyre will go flat and the functional emphysema will disappear

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[1] Goldman M J Principles of Clinical Electrocardiography Los Altos, California 1956

Plymouth W A LISTER

CHAIR OF DERMATOLOGY

SIR,—The statement in your annotation of Feb 1 that "at present there is no chair of dermatology in this country" surprises me A chair of dermatology (the Grant chair) was instituted at the University of Edinburgh in 1946

One assumes, of course, that "this country" is synonymous with Great Britain, and does not refer to the lower half of our island, latitudinally speaking!

Medical School Library,
Birmingham M P RUSSELL

*** We intended no distinction of latitude and we apologise for not taking into account the Edinburgh chair, which has been held since its inception by Dr G H Percival —ED L

ROLE OF PAPER ELECTROPHORESIS IN THE IDENTIFICATION OF HUMAN HÆMOGLOBIN VARIANTS

SIR,—The letter from Dr Lie-Injo Luan Eng (Dec 28) and the findings recorded by Schneider and Haggard[1] raise the question of the value of paper electrophoresis in the examination of human hæmoglobin variants

It has never been claimed that all human hæmoglobins could be identified by paper electrophoresis The method was introduced by Spaet[2] to demonstrate hæmoglobin C, which by this technique differed widely from the then-known hæmoglobins A (normal adult), F (fœtal), S (sickle-cell), and D It was clear from the beginning that this technique could not separate hæmoglobins A and F or hæmoglobins D and S Identification was based in the first case on differential denaturation by alkali, on spectroscopic analysis or on open-boundary (Tiselius) electrophoresis, and in the second on differences in the solubility of the ferro-hæmoglobin Later a marked difference was noted between the paper and Tiselius electrophoresis at alkaline pH of hæmoglobin A+G mixtures[3] On paper a good separation occurred but none was seen with the open-boundary technique This should not be surprising because cellulose is not an inert medium but contributes to the mobility of the hæmoglobins Without going through the whole list of hæmoglobins we should like to quote three more examples Hæmoglobins I and H behave identically on paper electrophoresis at pH 8 6 but differ at pH 6 5[5] Mixtures of hæmoglobins A+L, and A+a recently described "Galveston" type, behave alike on paper electrophoresis at pH 8 6, but differ on open-boundary electrophoresis[5]

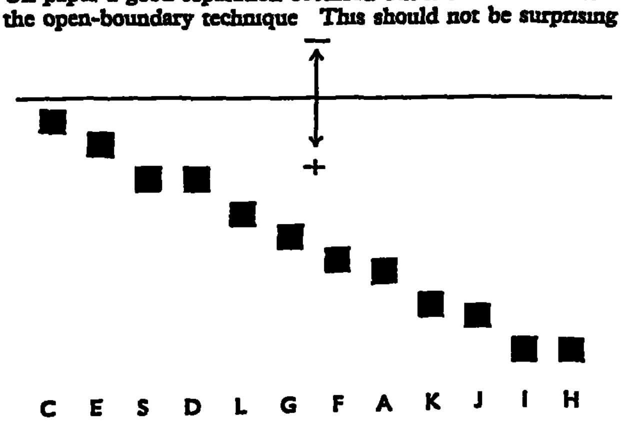

Fig 1—Scheme of mobility of the varieties of human hæmoglobin on paper electrophoresis at pH 8 6 The hæmoglobins which "overlap" cannot be separated. Their relative position must be assessed by running them side by side on the same paper strip

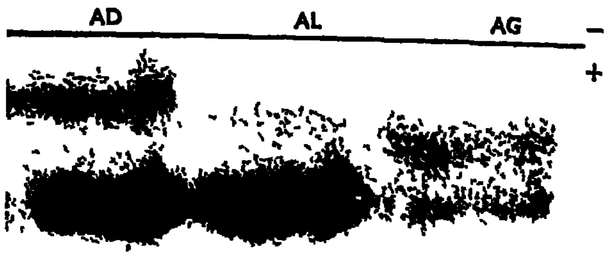

Fig 2—Separation by hanging-strip paper electrophoresis at pH 8 6 of purified solutions of the closely neighbouring hæmoglobins A, G, L, and D (For details of technique, see Lehmann and Smith[4]) The hæmoglobin bands were stained with Light Green dye

One of the most difficult problems is the differentiation between hæmoglobin E and the hæmoglobin A_2 fraction when the latter is raised in thalassæmia Both hæmoglobins behave alike on paper and starch electrophoresis whether at alkaline or at acid pH[6] Aksoy et al[7] have pointed out that difficulties may arise in surveys of populations where both hæmoglobin E and thalassæmia occur They suggested that a fairly reliable rule was that a hæmoglobin-E-like component present at a concentration below 20% was likely to be hæmoglobin A_2

Recently new techniques have done a great deal to ease the identification of hæmoglobins which are either alike or very similar in their electrophoretic behaviour Thus, hæmoglobin L which resembles hæmoglobins D, S, and G on paper electrophoresis at alkaline pH was found by Huisman to differ widely from them in its chromatographic properties Hæmoglobin mixtures A+D and A+S are identical when examined by electrophoresis or by chromatography,[8] but they can now be told apart by the new method of agar electrophoresis at pH 6 2[9] We have compared the hæmoglobin of a thalassæmia patient with the unusually high hæmoglobin-A_2 concentration of 10% with that of a hæmoglobin-E trait (AE) by these two methods At first we thought that there was a difference between the two on chromatography However, when the proportion of hæmoglobin E in the A+E mixture was lowered to 10% by the addition of hæmoglobin A, both the 10% A_2 and the 10% E mixtures behaved alike on chromatography Nevertheless, Dr V M Ingram has found in a preliminary experiment that hæmoglobins E and A_2 differ in their aminoacid sequences, as he has permitted us to quote

To return to Dr Lie-Injo Luan Eng's letter, it will be easily understood and no contradiction will be seen in her report that Professor Jonxis obtained on Tiselius electrophoresis a different order of mobility with her hæmoglobin from that she and others found by paper electrophoresis

It is true that hæmoglobins closely similar in electrophoretic behaviour may influence each other's mobility when mixtures of them are examined Thus a hæmoglobin A+F mixture will not separate on paper but the non-divided hæmoglobin may move a little more slowly than pure A and a little faster than pure F Pure hæmoglobin G will move just a little more slowly than the G in an A+G mixture, and so forth Nevertheless, whatever the limitations to the value of paper electrophoresis in the identification of human hæmoglobin variants it seems to us that its usefulness could be greatly enhanced if it were more often used to its best advantage The spectrum is becoming more crowded (see fig 1) and there is much to be said for the use of vertical rather than horizontal paper electrophoresis Hanging-strip electrophoresis has always been found to produce finer differentiation and more distinct and better reproducible patterns Application of the sample as a streak rather than a spot is necessary for good results (see fig 2) For instance, by this method we have not found Buginese X to change its mobility on dilution

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[1] Schneider, R. G , Haggard, M B *Nature, Lond* 1957, 180, 1486
[2] Spaet, T H *J Lab clin Med* 1953, 33, 975
[3] Edington G M , Lehmann, H., Schneider, R. G *Nature, Lond* 1955, 175, 850
[4] Lehmann, H , Smith, E B *Trans R Soc trop Med Hyg* 1954, 48, 12
[5] Rucknagel, D L., Page, E B , Jensen, W N *Blood*, 1955, 10, 999
[6] Kunkel, H G , Wallenius, G *Science*, 1955, 122, 288
[7] Aksoy, M , Lie-Injo Luan Eng, Lehmann, H *Lancet*, 1957, i, 792
[8] Huisman, T H J , Prins, H K *J Lab clin Med* 1955, 46, 255
[9] Robinson, A. R., Robson, M , Harrison, A. P , Zuelzer, W W *ibid* 1957, 50, 745

St. Thomas's Hospital, London, S E.1 — J A M Ager
St Bartholomew s Hospital, London, E C 1 — H Lehmann
Medical Laboratory, Stanleyville, Belgian Congo — J M Vandepitte

A DISTRICT MENTAL HEALTH SERVICE

Sir,—The "Worthing experiment", described by Dr Carse and his colleagues (Jan 4), may, as they claim, indicate a blueprint for future psychiatric practice We believe that domiciliary mental health services could be extended with advantage, indeed, a description of the development of such services will be found in the annu report for 1940 of the Bucks Mental Hospital It i however, necessary to guard against over-optimism about proposals which now seem to have captured publi imagination

In Worthing in 1956 there were 548 admissions in ten months from a catchment area with a population of 160,000, giving a crude annual admission-rate of 4 11 per 1000 In 1957 this rate was reduced to 1 68 per 1000 This measure of success is tempered by the knowledge that in England and Wales in 1954 there were 71,699 admissions from a population of 44,274,000, giving an annual admission rate of 1 62 per 1000, thus the second year of the experiment appears to have reduced the admission-rate almost to the level of national expectation It may be possible to effect similar reductions elsewhere if the general standards of home accommodation are equally good, and this tendency, if sufficiently widespread, might effect some reduction in the total cost of hospital care

Warneford Hospital, Oxford — R W Parnell, Ian Skottowe

A NEW SYNDROME

Sir,—Your leading editorial under this heading [1] concludes "But even if awareness of the new syndrome brings us no closer to solving the ulcer mystery, it has already helped us to define more clearly the extent of our ignorance"

The triad with the pancreatic islet-cell *adenoma* as the main feature does not appear to be very common according to either of the Zollinger and Ellison papers In the 1956 review of 24 such cases there were 19 malignant tumours and only 5 adenomas, and 5 of these 24 had evidence of hyperinsulinism and hypoglycæmia In regard to multiple endocrine adenomas, you failed to mention the case recorded by Fisher[2] and his subsequent explanation from results of injecting the serum of the patient into rabbits He concluded that no information from "clinical or experimental sources allowed for the interpretation that this substance (HGF) was directly related to ulcer production"

Hyperglycæmia and peptic ulceration seem to have an *inverse* relationship in patients with diabetes mellitus Further, as Ellison states in his later article "The role of glucagon is still in question. As I mentioned previously our studies have been rather inconclusive as to whether this pancreatic hormone has any effect on gastric secretion"

I agree that the presence of alpha-cell granules in one of the tumours described by Dr Priest and Dr Alexander[3] cannot be lightly discounted, but I wonder how important this is The beta granules in tumours are difficult to stain primarily, and yet the granules will readily accept the counterstain which is the usual method used in staining the alpha-cells In short, many cytoplasmic granules including those of the exocrine cells stain similarly to the alpha cells, both taking the counterstain

May I suggest, Sir, that meanwhile a question mark be placed behind the last word of the title of your leader?

Henry Ford Hospital, Detroit 2, Michigan, U S A — Joseph C Sieracki

PROBLEM FAMILIES

Sir,—The survey of problem families in London, reported by Dr Scott (Jan 25), raises a question of particular interest to us—namely, the contribution of low intelligence to social problems His conclusion is that low intelligence is an important ætiological factor in problem families, being present in 50 9% of his group This suggestion is of great importance, since if it can be shown that low intelligence bears such a causal relationship to problem families then the whole question of low intelligence must be seen in this light The analysis of results in the present study still leaves the point open to doubt since among the criteria for the selection of problem families were a number of qualities—"low intelligence" among them—on which the families were allotted points So long as low intelligence forms part of the definition of "problem family", inevitably the group will show low intelligence as a feature

May we suggest that the analysis should be taken a step further, using a standard for diagnosis of problem families which does not already use the criteria which the survey is designed to study The problem family, although greatly varying in individual characteristics, does have some common basic features, possibly more discernible than describable, which would permit of diagnosis by other means The factors listed by Dr Scott as supposed common concomitants could then be correlated with the problem families so determined If this were done the relationship of low intelligence, "emotional instability", &c, could be more clearly seen We suspect that low intelligence would not probably be found to be so markedly present In determining the presence of educational subnormality we consider also that a visual diagnosis is not satisfactory

Department of Social and Preventive Medicine, University of Manchester — Fraser Brockington, Zena Stein

TREATMENT OF MYXŒDEMA

Sir,—Though my article of Jan 18 was not particularly concerned with the significance of the B M R. test in myxœdema I am grateful to Dr Goldberg and Dr Seaman (Feb 1) for giving me an opportunity of explaining what I mean by a significantly lowered basal metabolic rate As I see it, the significance of the B M R in the syndrome of myxœdema is relative to the rest of the clinical details It has no absolute significance

In case 3 the fact of a previous thyroidectomy was of paramount importance to which the other facts must be subordinate The presenting clinical picture suggested a recurrence of hyperthyroidism and I expected that the B M R would show as it were, a swing to the right but it showed a swing to the left This could have been due to a technical error but the cholesterol level in the blood pointed in the same direction These findings were not in themselves conclusive evidence of hypothyroidism but the subsequent change in the T waves of the electrocardiogram after thyroid treatment added so much to their significance that I felt I was justified in including this case in my series The after-history has supported my opinion and to a clinician the therapeutic test is very convincing The same kind of reasoning led me to regard the B M R in cases 3 and 7 as significantly lowered

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[1] *Lancet* 1957, ii 1151
[2] Fisher, E. R., Flandreau, R. H *Gastroenterology* 1957, 32, 1075
[3] Priest, W M, Alexander, M K. *ibid* p 1145

The electrocardiographic changes are I believe in the same order of significance I would agree that their diagnostic value is limited and I have made no claim for more than this My conclusion was that their relation to the progress of myxœdema makes them of considerable value in controlling treatment I was interested to learn that Means found that 7 out of 24 patients retained their T-wave abnormality after specific treatment This corresponds closely to my own finding that in 3 out of 12 patients there was evidence of persistent heart damage

Oxford P C GIBSON

INFLUENZAL ENCEPHALITIS

SIR,—Our experience of influenzal encephalitis in the epidemic of 1953 and again in this present epidemic suggests that these cases, two examples of which were reported by Dr Dubowitz (Jan 18), cannot be so uncommon as was previously supposed Their incidence during these epidemics is too great for the association to be merely fortuitous

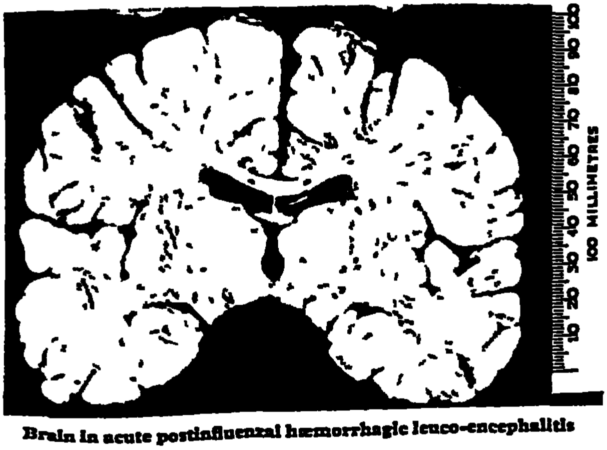
In 1953 of two patients one died, and in the past few months of three patients two have died, necropsy confirmed the diagnosis in all three fatal cases The ages of the two who recovered were 41 and 65 and of those who died 30, 37, and 56

There is invariably a history of influenza, and the encephalitic attack may occur in the relapse (relapse being common in our experience in this present epidemic) All patients, if conscious, present with very severe headache indeed, neck rigidity, drowsiness, and fever There may be early onset of coma, with asymmetry of signs involving the nervous system Bronchitis or bronchopneumonia was present in all The cerebrospinal fluid may or may not be abnormal in cells and protein, and there may be a neutrophil leucocytosis, though this is not invariable

If there is recovery, then it is complete within 10–14 days So far, no sequelæ have developed

There may be complete amnesia for the whole illness, with, in addition, some retrograde amnesia For instance, one of the patients who recovered remembers setting off to watch dog-track racing, but nothing more until he recovered consciousness in hospital days later

The macroscopic appearance of the brain (see figure) in patients who come to necropsy indicates that the previous hypothesis, that the condition is due to anoxia, is untenable The encephalitis (which is hæmorrhagic) is strikingly confined to the white matter This is in complete agreement with the pathological appearances described by Crawford,[1] and named acute hæmorrhagic leuco-encephalitis



Brain in acute postinfluenzal hæmorrhagic leuco-encephalitis

We are indebted to Dr W D Brinton and Dr H G H Richards of Winchester for referring one of the cases to us

Royal South Hants Hospital,
Southampton

R J McGILL
R A GOODBODY

MANIPULATION FOR BACKACHE

SIR,—Articles on manipulation of the spine always stimulate a mass of correspondence and Mr Bremner's contribution (Jan 4) is no exception Mr Thomas's letter of Jan 25 caught my eye He states "Of some hundreds of disc protrusions I have seen at operation I have never seen one that could be reduced by manipulation Perhaps it is only the irreversible discs that come to operation" He then asks the question "What evidence is there for disc protrusion reversible by manipulation?"

I thought it was generally accepted that at least 95% of disc lesions recovered with conservative treatment and only those that failed to do so came to operation This would explain why Mr Thomas has yet to see at operation a protrusion that could be reduced by manipulation

As to whether it is possible to reduce a nuclear prolapse by manipulation or traction so that it remains reduced depends upon the extent of the annular tear and the condition of the nucleus In the presence of a large annular tear and a turgid expansile nucleus, although traction may well reduce the prolapse with temporary relief of symptoms, it will obviously recur directly traction is released This is, of course, the type of case which does so well on sustained traction in bed and is quite unsuitable for manipulation If, on the other hand, the annular tear is small, the nucleus fibrotic, and its expansile power diminished, there should be much less tendency for the prolapse to recur after it has been reduced by traction Incidentally, as a treatment for nuclear prolapse traction is, in my opinion, the only safe manipulative procedure

Mr Thomas may argue that to suggest that a protrusion can be reduced by traction is pure surmise, and I can only reply that many patients, who have been diagnosed by, among others, orthopædic surgeons as having prolapsed discs, have responded to this form of treatment Actually one may ask what evidence is there of nuclear prolapse in the 95% of so-called disc lesions that recover with conservative treatment

London, W 1 E J CRISP

SIR,—Since the word "osteopathy" recently appeared in one of your original articles on the subject of manipulation, perhaps you would grant the courtesy of a rejoinder from an osteopath, since manipulative therapy is very much the osteopath's province

Mr Bremner (Jan 4) said that osteopathic manipulation was held out to be, by those using the method, a cure for virtually all backache Every qualified osteopath would strongly reject such an idea, and would cite many conditions illustrating the contrary There are, for example, the intractable referred pains of renal lithiasis, the disabling pains of spondylitis, osteitis deformans, multiple myeloma, and similar spinal diseases, and the specific infective types of spinal arthritis which spring immediately to the mind One could describe at length the systemic diseases which give rise to the symptoms of backache and which are not amenable to manipulative treatment Disseminated sclerosis, some nutritional deficiencies, and most neuropathies are amongst other cases in point The crux of this matter is, of course, accurate diagnosis

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[1] Crawford T J *clin. Path* 1954, 7, 1

Mr Bremner's statement that he applies manipulation for backache with the idea of giving the patient "a good start" will cause the average osteopath to recoil in horror As well suggest the victim be given a bath as a helpful preliminary

"Backache" is not a diagnosis, but a symptom Nor is manipulation an all-purpose procedure Indeed, it would be preferable to call it manipulative therapy, and when applied in a case presenting the symptom of backache it should be preceded by certain initial basic steps

Firstly, the patient must be clinically assessed, and an adequate differential diagnosis made Selectivity is essential

Secondly, when manipulative therapy is applied it must have specific objectives, work within well-defined limits, and never b used as a general procedure without definite reason

Thirdly, in manipulative techniques, it is necessary—to safeguard the patient and the parts involved—that the operator conforms to scientifically based rules Indiscriminate force is no more manipulation than a violent blow with a club on a ball is golf.

The trained osteopath claims that he uses his manipulative therapy to attain specific and precise objectives in a highly selective way He further claims that to use manipulative techniques, and the methods of diagnosis necessary as a preliminary to them, one must be taught and the period of training must be a long one A craftsman is much more than a man who just "knows how" To his theory must be added a long and sometimes difficult period of practical experience

London, S W 1

R. F MILLER
Registrar,
General Council and Register of Osteopaths

SIR,—Manipulative treatment presents us with a regularly repeatable and predictable series of events, and is therefore worthy of scientific study

A typical patient complains of pain of the "muscular rheumatism" type, and the appropriate manipulation of the appropriate joint commonly produces an immediate cure This is a phenomenon I have observed several times a week for the past ten years Although manipulation under anæsthesia is sometimes useful, I do not use it myself in general practice In any case, the question of anæsthesia is irrelevant to our present theme and is in fact confusing since it would be quite possible for a joint to be manipulated accidentally while an anæsthetised patient was being lifted or moved (I am thinking of the pains in the right iliac fossa which disappear after the removal of a normal appendix) On the other hand, I have several times seen patients whose pains have arisen from sustained, strained postures under anæsthesia

Some regard the manipulable diseases as being psychological in origin, and the treatment by manipulation as psychotherapy On the contrary, my own evidence suggests that we are dealing with a group of diseases of mechanical origin They arise generally either from a chronic postural strain (of external origin, such as those caused by sagging beds, pillows of the wrong height, or unsuitable furniture, or of internal origin, such as pregnancy backache) Alternatively, they may arise from acute strains, which may likewise be regarded as of external origin (such as backache after lifting) or of internal origin (such as postpartum backache, pain at the tips of the lower costal cartilages after coughing, or a "crick in the neck") The change in the degree of pain with movement in certain directions, and the usually successful mechanical treatment of such conditions by manipulation or by exercises, is further evidence of a mechanical disease

The precise nature of the changes in a joint which is being manipulated has not been certainly and clearly established I do not feel it is in any way disgraceful to admit to ignorance even over such a crucial point as this What we must all feel to be disgraceful is that ancient arguments about unregistered practitioners should have been allowed to obstruct the advance in knowledge of this part of medicine for the best part of a century

Lowestoft.

N B EASTWOOD

SIR,—I cannot understand how Dr Barbor (Feb 1) interpreted my letter of Jan 25 as advocating manipulation of the spine as a placebo There is nothing whatever in my letter to justify this interpretation

War Memorial Hospital,
Scunthorpe

DAVID F THOMAS

PENICILLIN HYPERSENSITIVITY

SIR,—During the symposium on antibiotics [1] and in your leading article on penicillin hypersensitivity [2] mention was made repeatedly of anaphylactoid reactions following injections of penicillin Dr Sims [3] asked whether anaphylactoid reactions to oily suspensions of procaine penicillin have been observed

Having dealt with the side-effects of antibiotics in a book,[4] I should like to draw your attention to the fact that in the literature it is stressed time and again that anaphylactoid reactions after penicillin depend neither on a special compound which is administered, nor on the medium in which penicillin is dissolved or suspended Reactions have been reported after oral administration of penicillin [5] as well as after local administration [6,7] Mayer et al [8] reported anaphylactoid reactions with fatal results due to inhalation of penicillin powder Everett [9] reported acute anaphylactoid reactions after instillation into the maxillary sinuses Special mention has been made [6] of anaphylactoid reactions after intramuscular injections of procaine penicillin in oil with aluminium monostearate In one case, the patient died 20 minutes after the injection Here it is remarkable that the case-history did not indicate any allergic reactions nor any previous treatment with penicillin

Jerusalem,
Israel.

LEO SCHINDEL.

CARE OF DRUG ADDICTS

SIR,—The report of a study group of the World Health Organisation on drug addiction (Jan 11, p 113) gives the impression that victims of addiction to opium and its derivatives can be readily treated by various techniques This is quite contrary to the general experience of those familiar with the problem

It is misleading and unrealistic to refer to "easiest to treat" and "harder to treat" and to suggest that addiction can be treated by mass methods (whatever that may mean) or by psychotherapy not essentially different from that employed in other personality disorders

The unpleasant truth is that drug addiction occurs invariably in psychopathic personalities, and is for all practical purposes incurable There is no such thing as a slight case of addiction just as there is no such entity as a slight case of pregnancy The condition either exists or does not and the only circumstances which can favourably influence the prognosis are its duration, the quality of the patient's personality, and the nature of his environment

Residential treatment is absolutely essential in any attempt at cure and anything short of this is a waste of time, effort, and money Furthermore, the addict will inevitably relapse after every treatment other than that carried out under residential conditions, which means that ultimately a longer-standing addiction will have to be tackled and that any confidence which the patient might have had in the efficacy of treatment will have become seriously undermined.

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[1] See *Lancet* 1957, ii, 888
[2] *ibid* p 929
[3] Sims, W H *ibid* p 1076
[4] Schindel, L Unexpected Reactions to Modern Therapeutics Antibiotics London 1957
[5] Pierce H E, Jr *J Nat M A* 1953 45, 68
[6] Feinberg S M, Feinberg A R *J Amer med Ass* 1956, 160, 778
[7] Blanton W B Blanton F M *J Allergy*, 1953, 24, 405
[8] Mayer C S Mosco M M Schutz, P J Oreman, F A, Steen L H, Baker, L A *J Amer med Ass* 1952, 151, 351
[9] Everett, R *ibid* 1951, 146, 1314

It is still far too easy for addicts to obtain drugs. In most cases they represent themselves to sympathetic (and possibly inexperienced) practitioners as anxious to undertake treatment because they can no longer afford the exorbitant prices demanded by dope pedlars. Very often drugs are obtained by people who are not addicts at all and the supply changes hands at fifty or more times its cost.

The only effective way of preventing abuses by ambulant patients or tricksters is personally to administer drugs only when there is clinical evidence of deprivation. They should not be given a supply of the drug under any circumstances but referred to hospital.

Until legislation is introduced to provide for the detention of addicts in hospital on their own application for a minimum period of three months, their numbers will not diminish and the cure of drug addiction will continue to be largely providential.

London, N.W.1 ELLIS STUNGO

TREATMENT OF UNDULANT FEVER

SIR,—With great interest I was reading Dr. Torres Gost's article of Jan. 25.

So many treatments have been tried for brucellosis—but none has been proved wholly satisfactory—it would be very welcome if 'Cathomycin' turned out to be the drug of choice.

I had the opportunity to observe several outbreaks of brucellosis in the Negev district of Israel. The first epidemic broke out some four years ago and we treated about 20 cases. In 1957, in a much bigger outbreak, we cared for well over 100 cases (a report has not yet been published). We had, of course, the opportunity to try several treatments. All patients, however, got streptomycin and chlortetracycline (aureomycin) or oxytetracycline ('Terramycin') in different doses and for different periods of time. The cases treated were all in an acute phase and showed the typical signs and symptoms of brucellosis in all varieties.

With very few exceptions, the patients reacted satisfactorily to this treatment: the temperature started to drop after about three days and usually became normal on the fifth day. All the other symptoms and pathological laboratory findings disappeared during the treatment. The spleen got smaller but did not return to normal. The treatment was usually continued for two to three weeks. I do not say that all the patients were cured during the course of treatment—several patients did have relapses—but quite a number felt fit after treatment. The follow-up showed no further relapses and there was a definite decline of the agglutination titre.

Dr. Torres Gost does not say anything about the follow-up of his patients, and I must confess his statement is not too convincing. One cannot yet say definitely whether cathomycin really is the drug of choice in brucellosis. Dr. Torres Gost does not mention how long his patients were observed after stopping treatment. It is known that patients with brucellosis can relapse even after months of comparative wellbeing. I should think a period of at least one year should elapse before the patient is regarded as cured. During this period the patient should feel well himself, the clinical and laboratory findings should remain normal, and the agglutination titre should become normal or at least decline.

The trial period of cathomycin seems to me too short to justify a final conclusion. Our experiences with streptomycin and aureomycin (or terramycin) were satisfactory as regards immediate reaction to treatment but not as regards complete cure after the first course of treatment. Practically all cases were finally cured. There were no toxic or allergic reactions to the drugs used.

Hayim Yassky Hadassah Negev Hospital,
Beer Sheba, Israel. E. E. LEHMANN

TIME OF RECURRENCE OR CURE OF TUMOURS IN CHILDHOOD

SIR,—The following case-report is of interest in view of Dr. Knox and Dr. Kingsley Pillers' paper (Jan. 25) on the prediction of a "period of risk" of tumour recurrence after operation.

A boy, born on March 14, 1953, appeared a normal child until August, 1953, when a large tumour was found in the abdomen filling the left hypochondrium and extending into the left inguinal fossa. On Aug. 26, at laparotomy, the tumour was removed. It was found to arise from the lower pole of the left kidney, and histological section showed that it was a Wilms tumour. Postoperative progress was excellent and no deep X-ray treatment was given. He was seen at 6-monthly intervals in the outpatient department and on Jan. 18, 1955, was noted to be fit and well. In February, 1955, he had an attack of pneumonia treated at home. Soon after this he became short of breath, and on April 4, 1955, a chest radiograph showed a large secondary deposit in the right lung. Further treatment was refused, and he died on April 27, 1955.

In this case the estimated "period of risk" was 14 months (5 months plus 9 months). This child survived 14 months after operation and a further 6 months into the "safe period" before a recurrence was found. Even if the attack of "pneumonia" is taken as the first sign of recurrence, he lived some 4 months into the "safe period" apparently fit and well.

As Dr. Knox and Dr. Kingsley Pillers point out, one patient surviving far into the "safe period" with eventual recurrence would seriously call in question the premise on which the estimation of the "period of risk" is based. This boy could be such a case. On the other hand, it is conceivable that a large secondary tumour could have been present in the chest for 6 months before it was actually diagnosed. Nevertheless, this patient's recurrence was sufficiently late to warrant some caution in accepting Knox and Kingsley Pillers' estimate of the "period of risk."

I should like to thank Mr. A. B. Birt for permission to publish this case.

Jenny Lind Hospital,
Norwich. M. W. PARTINGTON

CORTISONE AND HYPOGLYCÆMIC SHOCK

SIR,—Dr. Kay, in his interesting remarks,[1] expressed the opinion that in our experiments[2] insulin sensitivity was due to depression, by the previous large doses of cortisone, of the activity of the pituitary gland and the adrenal cortex. To explain the absence of hypoglycæmic shock during cortisone treatment, he suggested that the stimulating effect of cortisone on the cerebral cortex was absent at blood-sugar levels producing hypoglycæmic shock.

In our opinion, other factors must also be taken into account. The blood-sugar level at which insulin shock appears depends on the state of the organism. Under certain experimental conditions there is no shock at quite low blood-sugar levels, while under other circumstances shock may develop at comparatively high levels. In diabetic patients hypoglycæmic shock sometimes sets in at about 100 mg. per 100 ml., if, after insulin, the blood-sugar had fallen there from a high level.

In our animal experiments, when before insulin administration the blood-sugar had been considerably above normal (in rabbits the blood-sugar may rise spontaneously on excitation), insulin shock at times developed at a level even higher than

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[1] Lancet, 1957, ii, 850.
[2] Ibid. p. 805.

100 mg per 100 ml In other experiments the associated effects of insulin and stress sometimes induced shock at above-normal levels[3,4] On the other hand, in severe alkalosis in the symptom-free animal the blood-sugar level may be extremely low for long periods (1-2 hours) before convulsions supervene

These observations seem to confirm the supposition that under strong insulin effect the conditions impeding glucose utilisation may encourage the development of convulsions

Cortisone promotes rather than inhibits the uptake of glucose by the tissues[5] In our experiments the counter-regulatory and stress effects were inhibited, as Dr Kay has suggested, on the basis of the inhibiting effect of cortisone on the pituitary and adrenal cortex The above circumstances may explain why insulin shock did not develop after a pronounced fall of blood-sugar in cortisone-treated animals

1st Department of Pædiatrics
Budapest University Medical School.
L. BAR

HAZARDS OF INSEMINATION BY ELECTROPHORISED SEMEN FRACTIONS

SIR,—The possibility of artificial sex regulation in man is, of course, of general interest The success obtained by Schröder[6] in the electrophoretic separation and consequent insemination of rabbit sperm, since partially confirmed,[7,8] points to the possibility that a similar success may be obtained in humans, despite the negative result obtained by Kordts[9] and Pilz[10] My finding[11] that human sperms can be separated electrophoretically supports such a possibility It might be thought that there is an untrammelled path so far as the application of the electrophoretic method in artificial insemination is concerned But at the present stage there are serious hazards in such an investigation for the following reasons

(1) *Damage to sperms* —The electrophoretic separation can damage the sperm. Such damage is minimal with the " best experimentally determined, conditions in the narrow range of voltages and currents, which vary somewhat with donor and more with the history of the sperm, the pH, and the type, content, history, and temperature of the suspending buffer solution Generally, damage is estimated by observations on motility But I would add that experiments on sperms in this laboratory have shown sperm fatigue effects which are associated more often than not with peculiar behaviour and reduced motility even under " optimal " conditions The possibility cannot be excluded that such fatigued or damaged sperms, if allowed to fertilise the corresponding ova, may give rise to abnormal offspring I have noted occasional abnormalities in electrophoretic offspring of rabbits Since electrophoresis does affect the sperms, there is a distinct possibility that the proportion of abnormalities obtained on insemination with electrophoretic fractions will be greater than the natural proportion This aspect, along with other problems concerned in artificial insemination of non-human mammalian sperms, is being studied.

2 *Undesirable genetic selection* —Theoretical reasons can be advanced in favour of the hypothesis that the electrophoretic method—and other methods of sperm separation being investigated—are capable of genetic separation as well as sex separation. But what is not known and cannot be estimated at the present stage is what form of separation will take place. Some of the electrophoretic—and other—fractions may on artificial insemination give rise to undesirable characteristics in the offspring Only the results of study of a number of generations will decide

3 —*Undesirable chromosomal and other changes* —It is known that chromosomal material, being electrically charged, will tend to be displaced under the influence of electrical fields Such displacements are more pronounced when the cells are kept stationary, but cannot be safely neglected even in movable cells Such displacements may lead to undesirable irreversible genetic effects

Before the effects of such methods are studied in man, the hazards must be assessed in animals Neglect of the untoward possibilities places a grave responsibility on investigators attempting artificial insemination with electrophoretic fractions of human sperms, particularly so because other methods under consideration may prove less hazardous

Physical Chemistry Laboratory,
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London, E.17
S LEWIN

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[3] Barta L. Orv Hetil 1957, 98 248
[4] Barta L. Kísérl. Orvostudomány 1957, 9 430
[5] Fabrykant, M., Jackson, P. S., Ashe, B I Metabolism 1957, 6, 116.
[6] Schröder V N Z Tierz Zücht. Biol 1941, 50 1
[7] Lewin S To be published
[8] Gordon, M J Proc. nat. Acad Sci., Wash. 1957 43, 913
[9] Kordts, E. Z Tierz Zücht. Biol, 1952, 60 221
[10] Pilz A. [illegible]
[11] Lewin, S [illegible] 112, 549

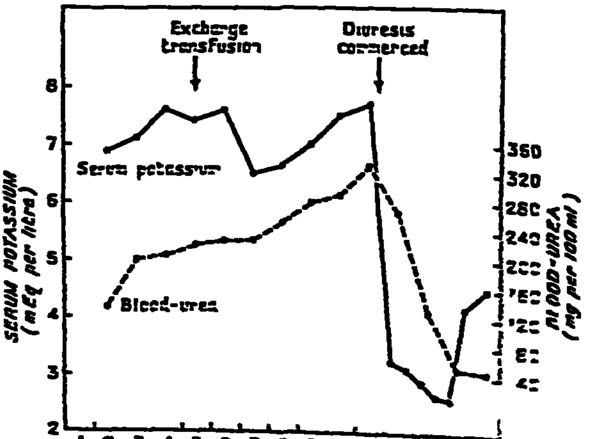
EXCHANGE TRANSFUSION IN THE MANAGEMENT OF ANURIA

SIR,—One of the greatest killers of anuric patients is hyperpotassæmia Bull's regime[1] of diet and fluid control has done much to improve the outlook, but situations still arise where a manœuvre which lowers the body-fluid potassium level for a few days may save life

When blood is cold-stored in citrate-glucose solution, potassium passes from the cells out into the plasma The plasma-potassium level rises from the normal 5 mEq per litre to 25 mEq, the cell-potassium level falling from 140 mEq per litre to 100 mEq When this blood is warmed at body temperature, the red cells take up potassium again, the cell-potassium level rising from 100 mEq to 130 mEq and the serum-potassium level falling by about 15 mEq per litre.[2] Thus stored erythrocytes soak up potassium from the surrounding medium, when warmed in the presence of glucose Therefore, in theory at least, if cold-stored packed cells separated from their plasma are transfused into a patient, they should take up potassium and lower the patient's serum-potassium level

In actual fact, simple transfusion of "packed" cells into anuric patients does not lower the serum-potassium level, possibly because of the high potassium content of the residual plasma medium of packed cells

A woman, aged 61, weighing 50 kg, was anuric following acute pyelonephritis in her sole functioning kidney When her serum-potassium level rose to 7 4 mEq per litre, exchange-transfusion was performed by taking off 550 ml of the patient's blood, and then running in 650 ml of packed cells through the same needle. After twelve hours the serum-potassium level had risen slightly to 7 6 mEq per litre, but after forty hours it had



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[1] Bull, G. M., Joekes A. M., Lowe, K. G
[2] Maizels, M J Physiol 1951, 112, 59

fallen to 6 5 mEq, and it remained lower than the pre-transfusion level for three days (see figure)

Profuse diuresis began on the eleventh day of anuria, and after energetic electrolyte replacement the patient made an excellent recovery

Why exchange transfusion should be successful when simple transfusion is not, I am unable to suggest, but I regard as significant this fall of 0 9 mEq per litre in the serum-potassium, and the long-continued effect of the transfusion in the presence of absolute anuria Such encouraging results are definitely worthy of further investigation The cells should be thoroughly packed by slow centrifugation The ideal material to use would be washed cells, where the plasma with its high potassium content has been completely removed

Edgware General Hospital,
Edgware,
Middlesex

P D HUGHES

INTRAGLOSSAL INJECTIONS A COMPLICATION

SIR,—Dr Bullough's short paper (Jan 11) suggested what appeared to be a useful route for injections when all the usual veins are inaccessible

Encouraged by his statement that he has used it for five years without mishap, I ventured to inject, as he suggests, 100 mg of suxamethonium into the tongue of a patient undergoing myomectomy The desired effect appeared in one to two minutes, and provided good relaxation during abdominal closure

Three days later, the patient complained of pain and swelling of the tongue This lasted for several days, and was accompanied by swollen, tender glands round the angle of the jaw on the left side and by some earache There was no pyrexia, but the pain and swelling subsided gradually under treatment with penicillin and 'Deguadin' lozenges At its worst, there was considerable œdema of the left side of the tongue, and the patient could not "put it out" between the teeth She was able to take only a liquid diet, and said she suffered more discomfort from the tongue than from her operation

It is difficult to be certain as to the cause of the swelling in this case Suxamethonium has been used intramuscularly on too many cases for a local reaction to seem likely The tongue is so vascular that a localised infection seemed at first unlikely, and the syringe and needle were from the usual sterile tray and the injected solution came from a freshly opened ampoule Whatever the cause or the rarity of such a reaction following intraglossal injection, there is no doubt that it causes far more discomfort and distress to the patient than the painful sequelæ of, say, intramuscular injections The use of an irritant solution, even in an emergency, by intraglossal injection would seem dangerous, since the resulting œdema might well obstruct respiration in the pharynx I personally feel disinclined to repeat the procedure with any solution

Altrincham, Cheshire

FRANK L ROBERTSHAW

COAGULABILITY OF THE BLOOD IN ISCHÆMIC HEART-DISEASE

SIR,—We were interested to read of the experiments of Dr McDonald and Dr Edgill[1] because of our somewhat similar work

We observed acceleration of coagulation in thrombophlebitis, hypertension, arteriosclerosis, and old myocardial infarction In these cases shortening of coagulation-time, Rosenthal's heparin clotting-time, and antithrombin-time, and acceleration of retraction were observed[2-4] In the thromboplastin-generation test higher thromboplastin curves than the normal were obtained

EFFECT OF HEPARIN ON FORMATION OF THROMBOPLASTIN

—		Before	Minutes after heparin					
			15	30	60	120	180	240
Maximal thrombo-plastin (%)	Normal	80-100	5	10	15	24	40	50
	Patient*	120	30	50	110	120	120	120
	Patient*	120	120	120	120	120	120	120

* Both with ischæmic heart-disease

In such cases we examined closely the result of the "heparin loading test" 100 mg heparin was given intravenously, 15, 30, 60, 90, 120, 180, and 240 minutes later venous blood was obtained for the thromboplastin-generation test of Biggs and Douglas We found that the maximal antithromboplastic effect of heparin in normal persons continued for 120-180 minutes, and then a subnormal curve was obtained

Using this method, different results were seen in Buerger's disease, thrombophlebitis, ischæmic heart-disease, and essential hypertension In some cases the antithromboplastic effect of heparin continued only 15-30 mins, and at 60 mins 100-130% thromboplastin was produced

In other cases, even 15 mins later the antithromboplastic effect of heparin was not seen (see table)

The experiments show that heparin was either rapidly consumed or quickly neutralised

Second Internal Clinic
of Istanbul University,
Guraba Hospital, Istanbul, Turkey

ORHAN N ULUTIN
D SESTAKOF

TREATMENT OF BREAST CANCER

SIR,—Your leading article last week deals once more with the radical-mastectomy *v* local-mastectomy-and-irradiation controversy in terms of alternatives and five-year survival-rates It had seemed to me that we had progressed beyond this point McWhirter performed a considerable service in challenging an oversimplified reliance on radical mastectomy as the one hope of cure for patients with carcinoma of the breast but offered in return at least as rigid a treatment scheme It is almost certain that he supplied better radiotherapy together with less dissemination due to restriction of the surgery attempted in the more advanced cases, showing a gain on balance but a loss whenever radical mastectomy remained the best treatment There has been a concerted attempt to throw doubt on McWhirter's results, which are far better presented than those of most of his critics—notably than those of the "strong challenge" you quote from the Mayo Clinic His recording and reporting are models which most would do well to follow, it is his conclusions and the practice they have led to which we are all entitled to debate I hold that no-one who has made a careful and unbiased study of the course of breast cancer should any longer believe that one simple treatment plan, applied rigidly by clinical stage of advancement alone, represents the best that can be done today for their breast-tumour patients

You refer to the improvement in five-year survival-rates with time In 1952[1] you published a lecture of mine showing that this had been occurring all over the world for many years irrespective of combination of treatment method employed I listed several factors other than treatment which might be responsible for this and added a plea for individual selection of treatment to suit individual people and circumstances, based on our considerable knowledge of the chances of success Much has appeared to support this view since then and to help us to better individual choice The over-riding importance to prognosis of tumour grade[2] has been even more securely established, the advantages of the utmost care in selection for radical mastectomy and the excellent results which then follow[3] have been stressed, the importance of age and tumour size[4] are better understood, and the influence of site of origin, length of history, and relation of onset to the menopause[5] have become a little clearer To these, and to many other factors in prognosis which influence the choice of treatment have been added the whole gamut of methods aimed at hormone control to stimulate our thought and keep us from rigidity in treatment planning

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[1] McDonald L, Edgill M *Lancet*, 1957, ii, 457
[2] Ulutin O N *Yeni Klinik Ilm*, 1955 1, 322
[3] Ulutin O N A Study of the Formation of Thromboplastin in Hæmorrhagic Disorders p 92 Istanbul 1957
[4] Ulutin, O N, Sestakof, D *Bull Soc turq Méd* 1957, 23, 699

[1] Smithers D W *Lancet*, 1952 ii 495
[2] Bloom, H J G, Richardson, W L *Brit J Cancer*, 1957, 11, 359

The Saskatoon experiment in education and organisation[6] has given new substance to belief in the value of early treatment with 70% of patients being first seen in hospital while still technically operable and with a five-year survival-rate of 44% rising to 48% (1944–49) in all patients seen without any of the usual exclusions, little of the usual selection, and using either radical mastectomy and postoperation irradiation or irradiation alone in many of the cases To compare methods of treatment merely by overall five-year survival-rates under circumstances differing so materially in other respects, as have those, for example, referred to above, is of little value

I am tempted to deal with the " humbling fact " tucked away in the Birmingham figures to which you refer but this raises other issues and would encroach unnecessarily on your space

Institute of Cancer Research,
Royal Cancer Hospital,
London, S.W.3

D W. SMITHERS

SITE OF FORMATION OF CASTLE'S INTRINSIC FACTOR: SPECIMENS WANTED

DR. K. B TAYLOR (Nuffield Department of Clinical Medicine, The Radcliffe Infirmary, Oxford) writes

" In this department we are interested in the site of formation of Castle's intrinsic factor and we need fresh frozen samples of the stomachs of patients with pernicious anæmia for prosecuting these studies These samples could be obtained during operations for gastric neoplasms If any of your readers could kindly inform me when an operation for carcinoma of the stomach in a patient with pernicious anæmia was about to be done, giving preferably a few days' notice, I could make arrangements for the collection of the specimen at the operation."

Parliament

QUESTION TIME

The Worthing Experiment

Dr DONALD JOHNSON asked the Minister of Health the cost of the Worthing experiment[7] in outpatient and domiciliary psychiatry for the 10 months of 1957 during which it had been operating —Mr R. H THOMPSON replied I am informed that the net expenditure in the first ten months of 1957 was £15,753 Part of the cost is met by a grant from the Nuffield Provincial Hospitals Trust.

Dr JOHNSON Is the Minister aware that two whole-time and one part-time psychiatrists, assisted by a small number of ancillary staff, have, during these months, reduced the number of admissions to mental hospitals in the Worthing area by 324 cases, compared with the same period last year, and will he make an actuarial investigation into the approximate saving of hospital costs thereby brought about, bearing in mind that a figure of £560 17*s* 7*d* per case is the average total cost of a patient between the time of admission and time of discharge? —Mr THOMPSON I am aware of the results reported in the first year of this two-year experiment, which I am watching with great interest. It is not possible to estimate any financial saving which may result, although there were fewer admissions to hospital, there was during the year no appreciable change in the number of patients resident in the hospital.

Smoking and Health Education

Mr MARCUS LIPTON asked the Chancellor of the Duchy of Lancaster if he would make a statement on the steps which he has taken to coordinate official information on the prevention of disease —Dr CHARLES HILL replied A number of Government Departments and other agencies are responsible for issuing official information on this subject. I keep in close touch with them, as they do with each other Mr LIPTON Is the Minister aware that much official information is now available on the connection between cigarette smoking and lung cancer? In view of the complete failure on the part of the Government in letting the public know the real facts by passing the whole subject to local authorities, will he reconsider the matter?—Dr HILL By statement in the House and by the activities of local authorities, directly and through the Central Council for Health Education, the facts on this subject are clearly and widely known. It remains for individuals to reach their own decision.

Mr E. H C. LEATHER With great respect, is it not a fact that the facts are still very much in dispute and that there are very strong grounds for thinking that the Medical Research Council has stuck out its neck much too far?—Dr HILL Although it is not a matter for me in my capacity as Chancellor of the Duchy of Lancaster, may I say plainly that the facts are clearly known? The case has been fully established.

Obituary

ROBERT KENNETH BOWES

M.D , M.S Lond., F.R.C.S , F.R.C.O.G

Mr Kenneth Bowes, surgeon to the obstetrical department of St. Thomas's Hospital, London, died on Feb 1 at the age of 53

His father, Dr J E Bowes, who lives in Cumberland, practised in Blackburn, and it was there that Kenneth Bowes spent his early years He was a scholar at Queen Elizabeth's Grammar School and a student at the University of Liverpool, qualifying M.B with first-class honours in 1929 In the same year he also took the M B Lond. with honours After holding house-appointments at the Liverpool Royal Infirmary he came to London, when he was appointed surgical registrar at St. Thomas's Hospital Before his appointment ended he had decided that his life-work was to be in obstetrics and gynæcology, subjects in which he had already as a student won a gold medal He successfully applied for the post of registrar to the department of obstetrics and gynæcology at St Thomas's From that time his course was clear and he moved steadily onwards till he was appointed surgeon to the department in 1936 He was also consulting surgeon to the South West Metropolitan Regional Hospital Board. He had held the posts of examiner in obstetrics and gynæcology in the Universities of London and Glasgow and to the Conjoint Board

Bowes' knowledge of medicine was encyclopædic and his memory was prodigious He read quickly and widely and was able to retain the substance of every article. This was an enormous help to him as the editor of *Modern Trends in Obstetrics and Gynæcology* It was said that his colleagues need never consult the *Quarterly Index Medicus*, for Bowes could be relied on to supply any reference He wrote well, clearly, and easily, and his published work included contributions to the *British Encyclopædia of Medical Practice*, Hutchison's *Index of Treatment*, and Birch's *Treatment of Medical Emergencies*

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[3] Haagensen, C. D Diseases of the Breast. Philadelphia, 1956
[4] McWhirter, R. J *Fac. Radiol.* 1957, 8, 220
[5] Smithers, D W Lecture to 58th Annual Meeting American Roentgen Ray Society 1957 (in the press)
[6] Watson, T A. *Surg. Gynec. Obstet.* 1957, 104, 106.
[7] *Lancet*, Jan 4 1958 p 39

A J W writes

With his great knowledge of all branches of medicine Bowes was a most able clinician and surgeon Loving his work he was loved by his patients He had the gentlest and kindest of natures If he thought ill of anyone, which is most unlikely, he certainly never said so, and his criticism of colleagues or of their work was always friendly He himself was the best and most helpful of colleagues In all his comings and goings he was quiet and unobtrusive He was apparently tireless and if anything too conscientious He saw so many possibilities that, in later years and especially when his health was not good, he worried himself over-much and often unnecessarily He was determined to carry on and to be his normal self His troubles he kept to himself, his desire was to help his patients and to do his work It is only now possible to imagine, if not to realise, the great mental and physical effort he often had to make

Handicapped probably by a severe illness in boyhood, at no time did he take any part in sport or games A most sociable person, he delighted in entertaining his many friends at home, where he and his wife were the best of hosts He loved his home and enjoyed working in the garden of his house near Guildford

It seems at the moment impossible to realise that he has gone from amongst us By those of us who worked with him he will never be forgotten

CHARLES JAMES SIDNEY O'MALLEY

C B E, M D Lond

Group-Captain O'Malley, who died on Jan 25, at the age of 57, was medical director of the Garston Manor and Camden Road Rehabilitation Centres, London, and regional adviser to the Ministries of Health and of Labour and National Service, deputy director of United Nations training-courses in Sweden, Finland, and Denmark, and consultant adviser on medical rehabilitation to the World Veterans Federation These responsible duties, which he discharged with human understanding, sound wisdom, and good common sense as well as joyful optimism and bubbling enthusiasm, were the outcome of his work throughout the years of the late war when he directed the mental and physical recovery of thousands of pilots, navigators, air-gunners, and ground staff

From the earliest days of the Battle of Britain these young men suffered not only multiple injuries—even as many as fifteen or twenty major fractures and dislocations, perhaps of all four limbs and spine, with nerve-injuries, wounds, and burns—but usually also the sense of anxious frustration, hopelessness, and fear Despite all this no less than 92% of pilots and air-crew returned to flying duty, 68% resuming full operational activities, and 84% of engineers, electricians, mechanics, and other ground technicians returned to their trades

Born in Melbourne, Australia, son of the late Captain O'Malley, D S O, James O'Malley was educated at Wellington College and St Thomas's Hospital He joined the Royal Air Force Medical Service soon after qualifying in 1925, serving at home and overseas especially in obstetrics and gynæcology When war broke out he was at the Officers Convalescent Hospital at the Palace Hotel, Torquay, until it was bombed Even then he infused into the older notion of convalescence a new spirit of active recovery He was principal medical officer in the Desert Force, in Sicily and Italy, and organised the air evacuation of 21,000 casualties Thereafter he was posted as commanding officer to the rehabilitation unit established at Loughborough College, where extensive playing-fields, gymnasiums, recreation rooms, and a swimming-pool formed the physical basis of treatment after surgical measures at Royal Air Force general hospitals He was appointed C B E in 1944

O'Malley took a large part in the development of all the rehabilitation centres of the Royal Air Force, and later he was also responsible for setting up in 1954 the Medical Rehabilitation Centre in Camden Road, London, which is believed to be the first outpatient reablement centre not attached to a hospital Today it treats some 80 patients a day Of O'Malley's work there J G S writes

The contribution which O'Malley made to the centre is inestimable His unfailing example to the staff, especially in the early days, was a deciding factor in its development He was not one to pay lip service to " team work "—he made sure that it existed and worked He believed that a high staff morale meant a high patient morale, and that both were essential to success The centre also *epitomises* his firm conviction that it is relatively unrewarding to treat disabilities A holistic approach to the problem is essential Successful medical rehabilitation is more of an art than a science

Of the warmth and affection with which Jamie O'Malley will be remembered R W -J writes

Even with a background of fairly rigid Service discipline he quickly found the right approach for men whose spirit as well as body was hurt and for whom a bold independence was essential For all his convivial friendship and benevolence, making him the life and soul of every party, on or off duty, he commanded discipline by inspiring loyalty, friendship, and confidence His eager enthusiasm and happy optimism was infectious Every patient, as well as every orderly, nursing sister, physiotherapist, and young surgeon, knew that he was to be trusted absolutely, and they obeyed him happily and willingly These qualities, together with industry and downright matter-of-fact sense, accounted for his success when he applied similar principles to the treatment of disablement in industry In this most important field of medicine he became an international leader

Dr O'Malley is survived by his widow and two daughters

Sir ERNEST KENNAWAY

Dr E H R Altounyan of Aleppo writes

I first met Kennaway when I entered the medical school of the Middlesex Hospital 45 years ago After that there could be no doubt in the mind of at least one young student that Truth existed amid apparent chaos and was well worth going for Crippled by a remorsely increasing disability which would have broken the spirit of most men, he proceeded to go for it, and in so doing inspired others A few weeks before his death, lying in hospital, he published his last article, taking physical pain as his thesis—the subject for study most immediately to hand He was a great cutter away of "dead wood" and certain aspects of religion were attacked by his incisive axe, but for me and—I think—for all who knew him well, he was the embodiment of true piety His friends know also that, but for the supreme devotion, domestic and technical, of Lady Kennaway, a tithe of his work would never have been accomplished

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Appointments

FOULDS, W S, M B Glasg, F R C S, D O part-time consultant ophthalmologist, Addenbrooke's Hospital and East Anglian Regional Hospital Board

GRANT, MONICA, L R C P E, D OBST, D P H assistant M O, Birmingham

MARTEN, R H B M Oxon M R C P part time consultant in dermatology, King's College Hospital, London

MATHEWS, E T, M B Birm, F F A R C S part time consultant anaesthetist, United Birmingham Hospitals

SEAGER, C P, M B, B.SC. Wales, D P M assistant psychiatrist, Bristol mental hospitals group

Notes and News

WORLD HEALTH ORGANISATION

THE Geneva meeting of the executive board ended on Jan 28 The budget for 1959—$14,300,000—was approved The International Fertility Association, International Union of Local Authorities, and Federation Internationale de Medecine Sportive were admitted to official relations with W H O

The budget for malaria eradication is $17 million in 1958 and the same in 1959—twice the 1957 budget. Eradication has almost been achieved in areas with a population of 231 million, is advanced in areas with a population of 43 million, has begun in areas with a population of 302 million, and is planned in areas with population of 580 million. In West Africa special factors hold up the programme. These include not only lack of funds and of trained workers and difficult communications but resistance to insecticides of *Anopheles gambiæ*, the chief vector, and its outdoor resting habit, and the drug-resistance of the parasites These difficulties were considered at a meeting in Brazzaville last November, which called for more entomological research and coordination of control and free exchange of information between research-workers and project staff

W H.O reports a continued downward trend in world notifications of plague—from 15,399 in 1951 to 514 in 1956 The figures for India in these years were 8230 and 44 respectively

EMERGENCY AMPUTATIONS

A NEW booklet produced for its doctors by the National Coal Board [1] will interest any doctor who deals with industrial accidents As Dr J Rogan points out in his foreword, it is rare for a man to be so trapped that amputation is needed to free him, but when the emergency arises great speed is required, and the doctor must know what he should do Mr W B Roantree deals briefly and simply with the ethics and the techniques, including anæsthesia (for which, he says, open chloroform is the only method practicable) and resuscitation, which should be given only when the patient is free, and only in hospital unless his admission will be much delayed The emphasis throughout is on the need for speed rather than the niceties of surgery, the booklet should prove of great practical use An appendix sets out the simple equipment needed

COFFEE POT CLUBS

THE first of these clubs was founded in London in 1954, chiefly through the efforts of Mrs H D R P Lindsay, J P, a fellow of Girton College, Cambridge, to give graduates and young men and women in the professions opportunities of meeting each other in pleasant surroundings and a congenial atmosphere.

There are now 3 clubs in London and 15 at towns in the Provinces, including Altrincham, Birmingham, Bristol, Cambridge, Cheltenham, Edinburgh, Exeter, Harlow, Leicester, Middlesbrough, Newcastle, Oxford, Plymouth, Rotherham, and Wolverhampton They have now 1000 members, including barristers, doctors, accountants, librarians, engineers, a bacteriologist, occupational therapists, an antiquarian horologist, and an orthoptist The age-limits are from 19 to 30, but there is a club in London for the over-30s. The subscription is usually about £2 a year The central feature is always a weekly at-home, and other activities are planned as desired by the members Information about the clubs can be had from the secretary, National Coffee Pot Committee, 108, Baker Street, London, W 1

University of Oxford

On Jan 23 the degree of B M was conferred on the following

Eugenia English Elizabeth M M Forstner N A Locke, J A Parsons, C. H. Smith (in absentia), M. K. Williams.

University of London

Dr Mary Barber has been appointed to the university readership in clinical bacteriology at the Postgraduate Medical School of London

University of Cambridge

On Jan. 25 the following degrees were conferred

M.B, *B Chir*—N F Leigh.
M.B—*A. M. Barnie-Adshead D G Beynon, Nigel Edwards, *R. C G Hughes, *Susan A Leaver, A. C W Lewis, P H. Rack, *M. W Riddall, C. E. R. Thompson, M. C Woodhouse.

* By proxy

University of Birmingham

On Dec 20 the following degrees were conferred

M.D—W T Smith.
Ch.M—G S M. Botha (with honours), J H Peacock.
M B, *Ch.B*—P I Akinboboye, G A L Bolt, George Evans, Chan Yong Lim, E. S Parry, B C B Pickles, P R. C. Randall, R. W M. Rees, Stella C Slade

Dr R. L Holmes has been appointed senior lecturer in anatomy

Royal College of Physicians of London

At a comitia of the college held on Jan 30, with Dr Robert Platt, the president, in the chair, Dr Donald Hunter and Dr G M Wilson were elected college representatives on the Joint Formulary Committee, Dr E. R Boland, Dr J B Harman, and Dr T C Hunt were re-elected representatives on the Central Medical Recruitment Committee

The following, having satisfied the censors' board, were elected to the membership

K. R Aberdour, M.B Lond., C. P Anyon M.B N.Z., Rosemary Ashby, M B Lond., Kathleen M. Barber, M.B Lond, Walter Beck, M.B. Cape Town, H. S Bedson M.B. Lond., F W Best, M.B. Lond., R. M Buckle M.B. Cantab, P J A. Butcher M.B. Lond., A R. Chrispin M.B. Birm., P J Dally, M.B. Lond., Esmond Davidson, M.B. Cape Town, P C. Farrant, M.B Brist., J K. Finlayson M.B. Aberd., Ronald Finn M.B. Lpool S B Furness, B.M. Oxon., P C. Gautier-Smith, M.B Cantab, P W Gilman, M.B. Manc., R. J Goetz, M.D Frankfurt, M.B Cape Town S/Ldr D N Gupta, M.B. Lucknow, M J Harris, M.B Sydney, W D Hayley, B.M. Oxon., William Hindle M.B Lond., I B Houston, M B. Manc., Geoffrey Howitt, M.B. Manc., J A. Ireland, M.B. Birm., R. A. Irvine M.B. Leeds, P H Kendall, M.B. Lond., A. V Kurtz M.B N.Z., A. F Lever, M.B. Lond., Kee Jin Lim, M B. Malaya B P Maclaurin, M.B N Z., Janet M Marks, B.M Oxon, David Mattingly, M.B. Lond. T O Ogunlesi, L. H Opie, M.B. Cape Town, E. H O Parry, M B Cantab Ruth Porter, M B. Edin., Isaac Rachman, M.B. Cape Town, Valerie J Richardson, M.B Durh., M L. Rutter, M.B Birm., J W Scopes, M.B Lond., Theodore Selby, M.B Sydney, A. K. N Sinha, M.B. Patna D R. Smith M.B. Durh, M L. Thomas, M.B. Cantab, C F H. Vicker, M.B Manc. Joanna M Ward, M.B Lond. P K. G Warren M.B Lond. E D West M.B Lond. D E. L. Wilcken M.B. Sydney, Verna Wright, M.D Lpool, N R. W Wynn-Williams, M.B. Lond.

Licences to practise were conferred on the following, who have passed the final examination of the Conjoint Board

Shirley A. P Abell, J R. Allan D L. Aspinall, K. A. Barlow, R D S Barnes, A. M. Barnie-Adshead, Elizabeth S Bates, Mary E. Braithwaite, D J Burgess J F Cam, Jean A Cam, A. R. O Chinery, W R. Chisholm-Batten, Alan Chynoweth M L. Clark, C. J Clemenson, G B Cornford, David Cowap, Alan Cox, Sheila M Creegan, Jane M. Critchley, C. W. Curnvan, G A W Dove J K. Duff Una M Dugan, T F Dunham, M K. Dunstan Peter Eckhart H J Edwards R. W Elsdon-Dew H C. Evans, P A Evans, D R. Firth Judith A. G Fletcher Mehroo Forbes, C. J Ford, George Hamler L. D Heap John Hellewell L. W H Hide, D I R. Higton Jillian M. Home Benjamin Howarth Rosemary J Huntley, P W James B F Johnson J M L. Jones, J E. Keithley Mary B Kelly, B S Kenner J R. Lane Patricia A. Las., J M. Laurent, G L M McLellan, Jean L. McNair S A. F O McNamara, C. K Manuel B S Mather, Harry Mendok, Lilianna Melzak, J C. Merrington, P V Meswani, A B J Miller-Williams, Gillian R. Montague D T Morris, P M. Morris, N P Nagpal T W Orwar K. M Patel, G R Peachey, B M Phillips, Sheila P I C. Phillips Alina T Piesowicz, H D W Plowright Betty L. Priestley A. K Ritchie Jeffrey Rawls, P A. Robson, B A. Ross, Valatham Rudralingam R. M I Shacksnovis, Nina Shorts, J O Sibthorpe, N A Simmons K. M Simpson D S Smith E O Sofowora J K. Stenham, Gillian Strube Ri H Sun P Teong Hwee Tay Diana Thornton R. E Teague D G Tranter, J N Tranter, Rita C. Travers, Pamela Walton, P J Whitfield D M L. Williams, Glenwynne Williams, Julia M. Winter, P J Wise, B J P Wright J E. C. Wright, R. J Young I I Zayid.

The following diplomas, and those mentioned in our issue of Jan 18 (p 170), were conferred jointly with the Royal College of Surgeons

D I.H—H. D R. Zscherpel.
D C.H—D J Clark.
D.M R T—Rodolfo Diaz Perches

On Tuesday and Thursday, March 11 and 13, at 5 P.M. at the college, Pall Mall East, S W 1, Dr Michael Kremer will give the Oliver-Sharpey lectures His subject will be Sitting, Standing, and Walking

Hospital Waiting-Lists

The number of patients in England and Wales awaiting admission to hospital at the end of each of the years from 1949 to 1956 was 1949, 498,000, 1950, 531,000, 1951, 504,000, 1952, 500 000, 1953, 526,000, 1954, 474,000, 1955, 455,000, 1956, 431,000 The latest figure, for Sept 30, 1957, was 434,000

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[1] Roantree W B Emergency Amputations National Coal Board Medical Memoranda no 13 December 1957 Pp 10 The board's address is Hobart House Grosvenor Place London, S W 1

Royal College of Physicians of Edinburgh

The college held the biennial dinner on Jan 24 Among those present were the Lord Provost of Edinburgh, the Secretary of State for Scotland, the Presidents of the Royal College of Physicians of London, of the Royal College of Surgeons of England, and of the Royal Faculty of Physicians and Surgeons of Glasgow, and the vice-president of the Royal College of Surgeons of Edinburgh, Dr J D S Cameron proposed the toast of the City of Edinburgh, and Mr Ian Johnson-Gilbert replied The toast of the Sister Professions was proposed by Dr. J K Slater, and the Rev Dr John Fraser and Lord Guest replied The Secretary of State for Scotland, Mr J S Maclay, proposed the toast of The College, which was answered by the president, Dr A Rae Gilchrist

Royal Appointment

Surgeon Captain R S Rudland, R N V R, has been appointed an honorary physician to the Queen in succession to Surgeon Captain Kirk Forsythe

International Congress of Psychotherapy

This congress will be held in Barcelona from Sept 1 to 7 Further particulars may be had from the secretary, Cátedra de Psiquiatría de la Facultad de Medicina, Casanova, 143, Barcelona, Spain

World Health Day

Each year the World Health Organisation sponsors World Health Day on April 7 In 1958, the tenth anniversary of the founding of W H O, Ten Years of Health Progress has been chosen as the theme of the celebrations

Naval Appointment

Surgeon Captain D F Walsh, R N, has been appointed medical officer-in-charge, R N Hospital, Malta, fleet medical officer on the staff of the Commander-in-Chief, Mediterranean, and medical adviser to the Commander-in-Chief, Allied Forces, Mediterranean, with rank of surgeon rear-admiral, in succession to the late Surgeon Rear-Admiral S G Weldon

Lady Tata Memorial Trust

The trustees of this fund invite applications for grants, scholarships, or fellowships for research on blood diseases, with special reference to leukæmia

Programmes of research on any aspect of malignant disease which may throw light on problems of leukæmia will be considered and awards may be made to investigators of any nationality, working in any country where payment can be made Particulars and application forms may be had from the secretary of the (European) Scientific Advisory Committee of the trust, Chester Beatty Research Institute, Fulham Road, London, S W 3 Applications must be submitted before March 31

Social Security Agreement with Australia

On Jan 29 Mr Harold Macmillan and Mr R G Menzies, Prime Ministers of the United Kingdom and Australia, signed a new agreement on social security

People who go from this country to Australia at present depend on their National Insurance record in the United Kingdom to qualify for Australian social-security benefits Under the new agreement their residence in the United Kingdom will count as residence in Australia and so enable them to qualify for Australian benefits The new agreement, which comes into force on April 1, will extend and simplify the reciprocal arrangements between the two countries

The new edition of the booklet *Everybody s Guide to National Insurance* (H M Stationery Office *6d*, postage *2d*) gives the new rates of contributions, pensions, and benefits

A new edition of the Ministry of Pensions and National Insurance's leaflet on maternity benefits has been published It contains the new rates of benefit Supplies are being sent to local executive councils

A delegation from the Yugoslav Ministry of Health is to examine British methods in the control of poliomyelitis and the production of the vaccine The visit has been arranged by the British Council

Diary of the Week

FEB 9 TO 15

Monday, 10th

UNIVERSITY COLLEGE, Gower Street, W C 1
5 30 P M Dr A Szent-Györgyi (Massachusetts) General Principles of Bioenergetics (First of two lectures)
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Prof John McMichael Heart Failure

Tuesday, 11th

UNIVERSITY COLLEGE
5 30 P M Dr Szent-Györgyi Applications of Bioenergetics (Second of two lectures)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Psychiatry* Dr G M Carstairs *Problems of Diagnosis in Patients from an Alien Culture*
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Prof J M Yoffey Problems of Lymphoid Tissue
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R W Riddell Differential Diagnosis of Mycotic Diseases of the Skin
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr Joseph Minton Ocular Manifestations in Clinical Neurology (First of two lectures)

Wednesday, 12th

UNIVERSITY OF LONDON
5 P M (Guy s Hospital Medical School, S E 1) Prof C H Waddington Evolutionary Adaptation to Environmental Stress
INSTITUTE OF DERMATOLOGY
5 30 P M Dr O L S Scott Genetic Principles
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr W P Cleland Benign Intra-thoracic Tumours
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *Pathology* Mr H Varley Corticosteroids—Their Determination and Clinical Significance (Presidential address)
ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Edinburgh, 8
3 30 P M Prof F A R Stammers Mechanical Factors in Post-gastrectomy Problems
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St Vincent Street, Glasgow
5 P M Prof Claude Rimington Aspects of Hæmoglobin Biosynthesis and Their Importance to Medicine (Walker lecture)

Thursday, 13th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr A L Cochrane Meaning of the X-ray Classification of Coal-workers' Pneumoconiosis (Marc Daniels lecture)
UNIVERSITY COLLEGE
5 P M Dr F H C Crick The Nucleic Acids—Structure (First of three lectures)
ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology* Mr L H Savin Functional Spasm of Accommodation Mr John Whitwell Pilocarpine in the Treatment of Squint Miss S Mayou Treatment of Fully Accommodative Convergent Strabismus
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Prof A Neuberger Enzymes in Health and Disease
INSTITUTE OF DERMATOLOGY
5 30 P M Dr O L S Scott Genodermatoses
ALFRED ADLER MEDICAL SOCIETY
8 P M (11, Chandos Street, W 1) *Dr I Frost* Sulphonamide Aids to Psychotherapy
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P M Dr J W Dundee *Man made Maladies*
UNIVERSITY OF ST ANDREWS, Queen s College, Dundee
5 P M Prof R E Tunbridge *The So-called Collagen Diseases*

Friday, 14th

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr Norman Tanner Diagnosis and Treatment of Œsophageal Bleeding
4 P M Dr A Rae Gilchrist Heart Block
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray s Inn Road, W C 1
5 30 P M Mr William McKenzie Stapes Mobilisation
MIDLAND CENTRE FOR NEUROSURGERY, Smethwick Hospital, Holly Lane Smethwick
8 P M Prof Alfred Meyer Fact and Myth in Prefrontal Leucotomy

The British Council for Rehabilitation, with the University of Aberdeen, will hold a course from March 25 to 27 on the industrial and social implications of rehabilitation The course is open to directors, personnel managers, hospital almoners, doctors, social workers, and all interested in rehabilitation The speakers will include Sir Hugh Griffiths, Dr T A MacQueen, Dr A A Eagger, Dr J M Wallis, Dr L A Wilson, and Dr I M Richardson Further particulars may be had from the general secretary of the Council, Tavistock House (South), London, W C 1

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THE PAPILLOMA AND ITS RELATION TO CANCER

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We define a papilloma as a branching or lobulated benign tumour derived from epithelium This definition excludes inflammatory lesions, warts, and polypi

Papillomata arising in the urinary and alimentary tracts, the ducts of the breast, and the skin has been studied to determine what relation they have to cancer We review here 215 cases of papilloma from King's College Hospital (K C H) seen by the general surgeons from 1948 to 1956

The Series

PAPILLOMA OF URINARY TRACT

Papilloma of Kidney and Ureter

Papilloma of the renal pelvis constitutes about 3% of all renal tumours (Riches et al 1951), and only 52% of patients survive five years after having had nephrectomy for it (McDonald and Priestley 1944) We report from K C H 2 cases in one there were seedling papillomata down the length of the ureter, and the other was associated with a staghorn calculus Both growths were benign Papillomatous disease of the renal pelvis is rare and bilateral disease even rarer One of Macalpine's (1947) patients was a dyeworker thought to have true primary growths on each side and in his bladder Tumour cells may be found in the urine, and it is important, when carrying out nephro-ureterectomy, not to contaminate the wound, lest implantation take place Macalpine (1947) found that benign papillomatous material implanted in the wound always became malignant

Papilloma of the ureter is rare Moore (1942) noted that less than 60 cases had been reported We report 3 cases from the K C H series, of which 1 has been mentioned above, and the 2 others were solitary growths at the lower end of the ureter These conformed, as did those of Wiggins-Davies and Elwood (1952), with the statistical observations of Scott (1943) that these tumours occur most commonly in the lower third of the right ureter

Papilloma of Bladder and Urethra

The K C H series provided 119 cases 76% were in males, of whom 60% were over the age of 60, and 24% were in females, of whom 75% were over the age of 60 There were no cases in women under the age of 50 67% of the growths were close to or at the ureteric orifices, 33% being on the right side and 34% on the left 11% were near the internal meatus

Most of these cases followed the usual clinical course of treatment with resultant cure or periodic recurrence From the remainder come two facts of interest

Firstly, there were 6 cases which to some extent refute the idea that malignant bladder tumours are always malignant from the outset In each of these 6 cases biopsy, when the growth was first seen, showed that the tumour was benign Subsequently, in most cases from three to five years later, biopsy of the recurrent tumour showed it to be malignant 2 of these cases are of particular interest because, during the period between taking the initial benign biopsy specimen and taking the later malignant biopsy specimen, the tumour recurred—three years after the initial treatment Further, both simple and malignant recurrences were at or very near the site of the original growth The second point of interest was that 4 of the cases (3 6%) had coexistent or almost coexistent carcinoma of the sigmoid or the descending colon These 4 patients were over the age of 60, 3 being women

Papilloma of the urethra is rare, apart from those on the glans penis, which are probably infective in origin, for they are contagious and spread rapidly after being disturbed by circumcision Those of the anterior urethra may also be infective Those of the posterior urethra are transitional-cell tumours and similar to bladder tumours Some of these may be papilloma seedlings which have become implanted after instrumentation for the treatment of bladder growths (Ashworth 1956) Riches (1944), however, described 3 cases of papilloma in the posterior urethra in which the bladder and upper urinary tracts were clear of growth

PAPILLOMA OF ALIMENTARY TRACT

Mouth and Pharynx

Although the K C H series is small (7 cases), papillomata on the lips and in the buccal cavity are not uncommon Mostly the growths are in the middle-aged or the elderly, they are usually single, but are sometimes accompanied by a "kissing" or contact growth, a papilloma on the lower lip having its smaller counterpart on the upper lip, as in 1 of our cases

Growths of the oropharynx are said to be relatively rare, New and Childrey (1931) reported 35 cases in which the distribution of the growths was almost equal between the fauces, the tonsils, and the soft palate Similar figures were found by Henner (1942), who reported 94 cases among 25,000 patients examined

Papilloma of the œsophagus is extremely rare

Stomach and Small Intestine

The villous papilloma of the stomach, of which there are 51 published cases (Walk 1951), has not been consistently differentiated from the ordinary polyp Willis (1953) regards the adenoma and the papilloma of the stomach as varieties of the same tumour Walk found that the incidence of malignancy was high in these villous tumours, the rate of eventual malignancy being highest (72%) in the age-group 61–70 Some of these tumours grew to a considerable size and still showed no evidence of malignant change These growths not only tend to become malignant but are often associated with carcinoma, in Stewart's (1931) series of 56 stomachs containing benign epithelial tumours, cancer was also present in 27%

Simple tumours of the small intestine are rare, but the adenoma is the least rare It is commonly single and more often pedunculated than sessile Papilloma of the jejunum has presented clinically as melæna and anæmia (Hunnicutt 1952) From a girl of 15, admitted as an emergency, one of us removed a papilloma in a Meckel's diverticulum which had produced an intussusception A papilloma may arise in heterotopic gastric epithelium in the diverticulum One such growth was composed of benign adenomatous tissue containing both gastric and duodenal glands (Schullinger and Stout 1934)

Papilloma of Gallbladder

Papilloma of the gallbladder presents often as cholecystitis, sometimes with biliary colic A cholecystogram often shows a normal gall-bladder as regards function, but there may be a filling defect produced by the papilloma, which is sometimes pedunculated The biliary colic is attributed to attempted passage of the papilloma down the cystic duct (Lund and Burman 1951) In a case described by Griffiths (1956) the patient had severe biliary colic accompanied by transient jaundice due to obstruction of the common duct by numerous small pieces of growth exuded from the cystic duct

These papillomata are rare 8 were found in 2000 cholecystectomies, and coexistent gallstones were found in only 3 of these cases (Kane et al 1952) Although Mayo (1915) and

Irwin and MacCarty (1915) described a large series of lesions which they considered to be papillomata of the gallbladder, Kerr and Lendrum (1936) suggested that many of these were probably cholesterol polyps

There is no established view about the relation between papilloma and carcinoma of the gallbladder Although Shepard et al (1942) believed that the papillomata rarely became malignant, Tabah and McNeer (1953) hold that papilloma of the gallbladder is a precancerous lesion, and they describe examples of the true papilloma having histological evidence of malignancy within the papilloma in 3 cases

Papilloma of Rectum and Colon

In the K C H series were 31 cases of papilloma of the rectum, 55% being in males whose average age was 56 The average age of the females was nearly 10 years older The papilloma or villous tumour of the rectum is of two types, the sessile and the pedunculated Each has a convoluted surface formed by villi closely packed together (Ewing 1950)

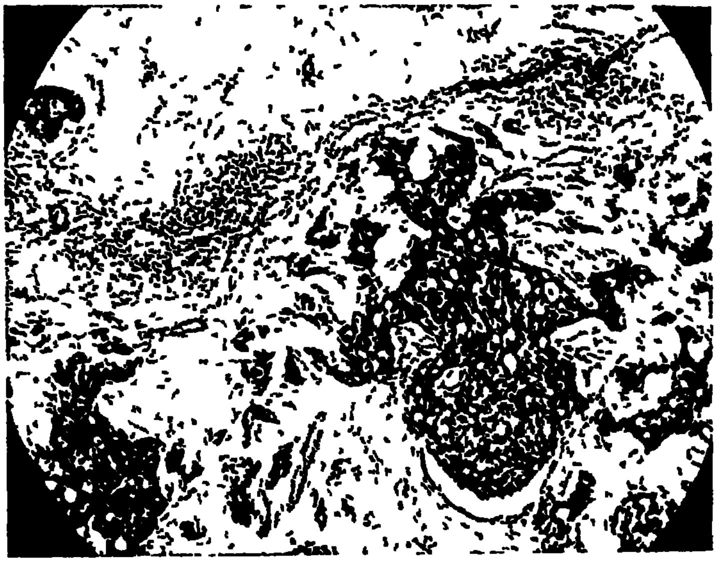
Fig 2—Deeper portion of section shown in fig 1 Note infiltration

It has been customary to divide the simple epithelial tumours of the bowel into two distinct entities, the adenoma and the papilloma Dukes (1947) first pointed out that the adenoma and the papilloma are not distinct and separate growths but variants of the same neoplasm He suggested that the difference in form depends, on where the most stimulation to the epithelium is received If the stimulation is on the surface of the mucosa, the tumour will be villous because there is room for it to grow, but, if the stimulation is at the bottom of a crypt, the tumour will be pedunculated because space to grow is limited Dukes has since suggested (1957) that the frond-like form of the papilloma of the bladder or bowel may be produced by the muscular contraction of the wall of the viscus forcing the tumour towards the centre of the lumen

In the K C H series 61% were single growths, 23% were multiple, and 16% encircled the bowel sufficiently to warrant a major resection The theory of the multifocal origin of such tumours was supported in that in some cases from which a benign growth had been removed a second growth was found later in a position proximal to that of the first Seeding as a method of spread was therefore unlikely

As regards evidence that these growths are precancerous, only 3 of our 31 cases were associated with eventual malignancy, 2 of these are examples of where a papilloma which is clinically benign is removed, and, although histological examination shows it to be a carcinoma, there is no recurrence, simple removal being apparently adequate

One of these cases was in a woman, of 63, from whom a papilloma was removed three times in three years Two years after the last removal a fourth tumour was found at the same site and was also removed, but this time it was malignant and a major resection was carried out Examination of the specimen showed that the removal of the initial growth had been complete, and there was no evidence of remaining malignant growth or metastases

The second case was in a woman of 54 who had a number of rectal papillomata, some of these were benign, but others, whose appearance on sigmoidoscopy in no way differed from the rest, contained areas of carcinoma (Dukes' grade II) within the benign growth As there was some doubt as to whether they were primary carcinomata or malignant change in a previously benign lesion, it was felt that the patient should be kept under observation after local removal of the tumours rather than be submitted to an abdominoperineal operation, which was the only alternative Two years later there has been no recurrence

The third case illustrates the opposite situation A papilloma was removed from a woman of 62, but in the follow-up another growth was found which had not been present at the initial examination Histological examination of two biopsy specimens showed a benign papilloma, but that of a third showed a poorly differentiated carcinoma A major resection of the growth was done, and the operation specimen contained three growths The most distal growth was a benign papilloma, above this was a sessile (Dukes' grade III) carcinoma, and the most proximal of the three was a pedunculated adenoma containing an area of well-differentiated carcinoma

Sunderland and Binkley (1948) reported a series in which 68 7% of papillary adenomata showed areas of cytological carcinoma either in the original tumour or in a recurrence at the site of removal, but only 39 5% developed invasive properties These workers point out that it is difficult to argue with those who maintain that those tumours which subsequently develop infiltrative properties must have been carcinomatous from the beginning because it is impossible to make serial sections of these growths, and therefore no definite conclusion can be drawn It would be unreasonable, however, to maintain

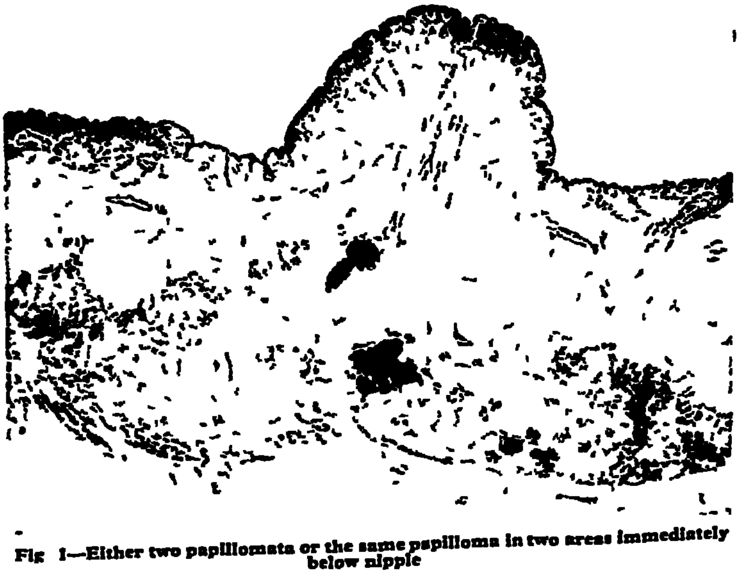
Fig 1—Either two papillomata or the same papilloma in two areas immediately below nipple

that a tumour which was a carcinoma from the beginning would recur superficially at irregular intervals and suddenly invade, metastasise, and cause death

The disease known as familial intestinal polyposis is usually regarded as an entity, probably because of its striking mendelian characteristics rather than its pathology Although the lesions are predominantly of the adenoma type, as Dukes (1952) states, they are another variety of the same neoplasm as is the papilloma, and papillomatous tumours are sometimes found side by side with the adenomata (Lockhart-Mummery et al 1956) The incidence of malignant change in this condition is high, and cancer is most likely to be discovered about fifteen years after the first onset of the symptoms of polyposis—i e., at about the age of 35 About 75% of patients with polyposis, if untreated, will develop cancer

DUCT PAPILLOMA OF BREAST

As pointed out by one of us (Wakeley 1945, 1947), there is too great a tendency today to regard duct papilloma of the breast as malignant, or potentially malignant, and therefore requiring amputation of the breast This idea shows a lack of thought, of experience, and of a thorough examination of every breast removed Local amputation of the breast is an easy operation and it is wishful thinking to say that, because a young woman has a bloodstained discharge from the nipple, her breast should be removed because cancer might supervene Of our 49 duct papillomata of the breast only 1 showed evidence of malignant change (figs 1 and 2), and a bloodstained discharge from the nipple may be caused by carcinoma, by chronic cystic mastitis, or by papilloma

Duct papillomata are nearly always found in the larger ducts and therefore are situated beneath or near the nipple or the areola They can be excised through a radiating incision over the enlarged duct. Where an enlarged duct cannot be palpated, the nipple can be covered with collodion for two or three days, during which time the blood will accumulate in the duct and distend it, rendering it palpable

Conservative surgery should be practised for duct papilloma of the breast, but a "follow-up" is necessary to prevent missing the odd case which might become malignant later

CUTANEOUS PAPILLOMA

The papilloma of the skin has been defined as a tumour-like proliferation of the skin characterised by hyperkeratosis According to this definition the following would be classified as papillomata nævus verrucosus, the seborrhœic wart, senile keratosis, verruca vulgaris, and acanthosis nigricans These conditions may appear similar in that they are papillary, but detailed dermatological and histological examination shows them to be distinct

Nævus verrucosus may be single or multiple and is usually present at birth, it is benign The *seborrhœic wart* or basal-cell papilloma is often mistaken for a malignant melanoma because of its colour, which varies from yellow to black, it, too, is benign *Senile keratosis* occurs in the elderly, usually in patients over 60, the lesions being on the sites of exposure, commonly the face and the hands About 20–25% of these growths are said to develop into squamous-cell carcinoma

The two remaining clinical conditions are of more interest to the surgeon *Verruca vulgaris* is the commonest example of a histological papilloma It is believed to be caused by a virus, the lesion being commonest at the sites of trauma, especially the hands and knees, but it may occur in old operation scars Virus-like particles have been obtained from some of these growths, which are distinguishable cytologically in that the cells contain eosinophil inclusion-bodies and vacuolated cytoplasmic masses (Bunting et al 1952) The nuclear enlargement, distortion, and interference in the development of the epidermal cells probably reflect the effect of the virus

Acanthosis nigricans occurs in two varieties, benign and malignant The malignant is of surgical interest because, in half the cases occurring after middle age, the skin lesion, although benign, is associated with malignant disease elsewhere, usually in the alimentary tract, most commonly in the stomach (Curth 1943)

Of our K C.H series of 46 cases of cutaneous papillomata removed by surgery 34 (about three-quarters) were on sites of exposure, on either the face or hands The combined average age was 59, the average age in the males being slightly less 1 papilloma showed evidence of early malignant change

Discussion

In attempting to assess the relationship of the benign papilloma to cancer we have sought for the common factors in the pathology and ætiology of papillomata in different parts of the body

INCIDENCE AND SITE

With the exception of the virus papilloma, most papillomata in all sites occur in people over the age of 50 There is little difference in the incidence in the sexes except as regards the urinary tract, where the disease is predominantly in the male In our series there was no papilloma of the bladder in women under the age of 50

There may be a relationship between the sex hormones and acanthosis nigricans, Curth (1943) suggested that, in the benign type the skin lesion may be activated by one of the sex hormones, for the benign lesion is usually found in a young patient and appears at puberty, or, if already present, tends to spread at this time

If the papilloma is caused by some stimulant, one would expect the growths to be most common at sites of exposure This is probably true of growths on the skin (three-quarters were on sites of exposure) and the bladder, and to a lesser extent for those in the alimentary tract, except perhaps the rectum In the mouth the growths are commonest on the pillars of the fauces and on the soft palate, which are perhaps the sites most easily affected by trauma and a stimulant The adenopapilloma of the alimentary tract is most often found in the rectum, and it is possible that, here again, the stimulant has the greatest opportunity of access, because not only are the fæces harder and more traumatic at this point but stagnation is greater here than in the upper reaches of the bowel In the bladder the papilloma is most common near the ureteric orifices There is some similarity in the figures from clinical and experimental sources in 67% of cases in the series the growths were near the ureteric orifices, and in animals in which bladder tumours were artificially induced by feeding with B-naphthylamine 30% of the growths were on the lateral walls and 33% on the posterior wall of the bladder (McDonald and Lund 1954) Kaplan et al (1951) have pointed out that lesions which involve the ureter are most often found at the anatomical points of narrowing

PATHOLOGY AND PATHOGENESIS

From the work of Dukes (1947, 1952) and Willis (1953) it is evident that the adenoma and the villous papilloma of the stomach, intestine, and rectum are not separate tumours but variations of one neoplasm In considering how these tumours are formed and what relation they bear to cancer three questions arise

(1) *Is the Papilloma Precancerous and, if so, is it Malignant Initially ?*

Clinical and experimental work shows that the papilloma is a potential source of cancer Clinically it is difficult to determine which of these growths will become malignant, and sometimes it seems that, in the long run, the clinical assessment of malignancy may prove more accurate than the histological examination One can only repeat what has been said before some of these benign growths will remain benign, some will become malignant soon, and some will have malignancy thrust upon them In some tissues a papilloma tends to become malignant rapidly, and one suggestion is that such tumours do not undergo transition from a benign to a malignant state but have concealed malignancy from the beginning of their growth This may be true of some but not every such tumour, because there is ample evidence that malignancy may develop in a lesion which has been benign for many years, and some benign neoplasms contain a focus of carcinoma which is not invasive Macalpine (1947) supported the teaching of Dukes a urinary papilloma may be benign in one part and malignant in another, and a papilloma may be malignant but not necessarily invasive

(2) *How do Multiple or Successive Growths Arise?*

Benign and malignant lesions may arise side by side, suggesting that the whole area contains foci of potential tumours Experimental work on the bladder and the gallbladder shows the same thing

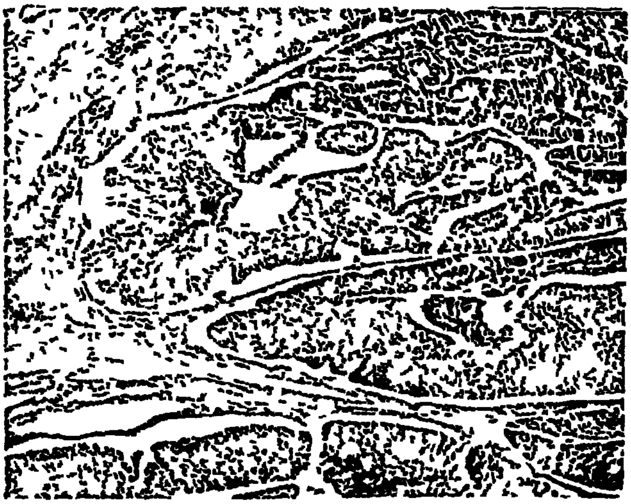

Fig 3—Transitional-cell papilloma of bladder

Bonser and Jull (1956) implanted a chemical carcinogen into the bladders of mice for about a third of their life-span and produced a variety of epithelial change varying from hyperplasia to frank carcinoma So the question whether carcinoma is preceded by a graded series of epithelial changes or not was again raised by these experiments These workers conclude that, although some cancers arise in benign lesions, others appear to arise spontaneously, but in nearly all the bladders there was evidence of epithelial hyperplasia Though many bladders contained only a single tumour, there was adequate evidence of the multifocal origin of cancer

Similar results were obtained in cats' gallbladders in which carcinoma had been induced by implanting within the gallbladder a single pellet of methylcholanthrene (Fortner 1955) Papillomata were found together with carcinoma, and, although the carcinogen was applied to the entire surface of the gallbladder, malignant change did not take place uniformly, and benign epithelium was seen adjacent to malignant

Although there is evidence that multiple growths may arise from multifocal areas of neoplastic change, this is not the only method of growth, spread may still take place by transplantation and implantation Exfoliated cells from tumours of the bowel may become implanted on the suture line of an anastomosis, and cells from a papilloma of the urinary tract become implanted in the wounds and sites of instrumental trauma Experiments have also shown that exfoliated growths can become implanted in intact bladder epithelium where there is stagnation of urine

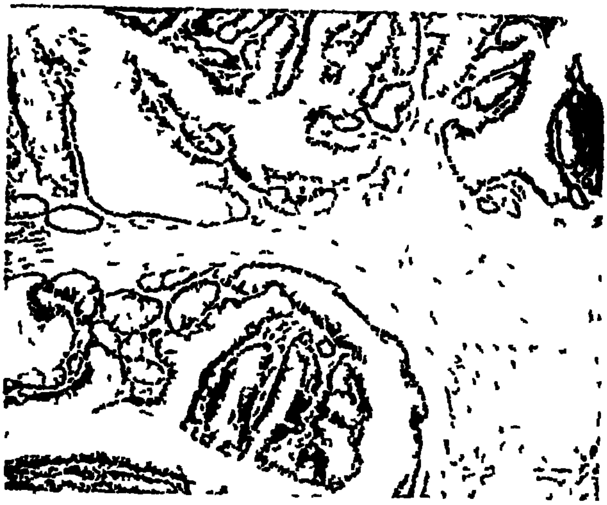

Fig 4—Benign adenoma of rectum

McDonald and Thorson (1956) made "Pavlov pouches" in the bladders of dogs in which there would be stagnant urine and placed in them loose fragments of papillary growths induced in other dogs fed with β-naphthylamine In 3 of 7 dogs the growth became implanted in the intact bladder epithelium These papillary tumours resembled their progenitors microscopically and were regarded as papillary carcinomata

Marcus (1953) described a case in which stagnation of urine may possibly have played a part The patient had a scrotal cystocele in an inguinal hernia which had been present for twenty-five years The cystocele contained three benign papillomata, but there was none in the remainder of the bladder

(3) *How is the Tumour Initiated?*

Clinical and experimental evidence shows that an area of tissue may undergo neoplastic change varying from hyperplasia to invasive malignancy The variety of these epithelial changes postulates that the stimulation which produces them must vary either in kind or in degree

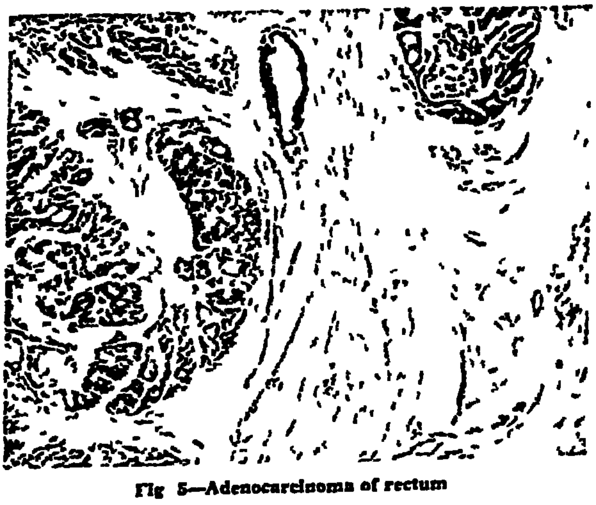

Fig 5—Adenocarcinoma of rectum

In the skin the change may be produced by a virus in adolescence, but the growths of the elderly suggest that the stimulant may take a considerable time to produce its effect This may also be true for the papillomata of the alimentary and urinary tracts Experimental tumours have been produced in the urinary tract by chemical stimulation This raises the question whether similar stimulation may take place in the bowel by breakdown products of bile or of food

Boyland et al (1955) found a high level of glycuronidase in patients with bladder growths and in patients who, as the result of treatment, were clinically free from growth. They suggest that an enzyme present in unusual abundance may liberate a carcinogen from the urine.

Holsti and Ermala (1955) painted with tobacco tar the lips and mouth of mice to study its effect on the oral mucosa No local change was produced, but 52 of 60 mice had papillomata in the bladder, mainly near the trigone. In 6 mice malignant change had occurred at the base of the papilloma The control mice developed no tumours, nor did this strain exhibit tumours spontaneously

Further evidence has been produced that substances which stimulate tumour formation are excreted in the urine

McDonald and Lund (1954) made "Pavlov pouches" in the bladders of dogs so that the mucosa of the pouches was excluded from contact with urine The dogs were then fed with β-naphthylamine Papillary growths of transitional carcinoma developed only in those portions of the bladder which were in contact with urine.

A man, aged 69, with gross papillomatosis of the bladder underwent total cystectomy and transplantation of ureters in 1953 (Parker 1957) Three years later he was found to have a papillomatous growth in the bowel below the level of the ureteric openings The operation specimen contained two growths, a poorly differentiated adenocarcinoma and a benign rectal papilloma (figs 3-5)

Although neoplastic change in all its phases can be produced by direct chemical stimulation, this process may be complicated in that more than one stimulus may be involved

Urethane was painted on the skin of mice, but no tumours were produced, repeated applications of croton oil alone produced very few tumours, but the application of urethane followed by repeated applications of croton oil (Salaman and Roe 1953, Roe and Salaman 1954) gave rise to many epidermal tumours, some of which were malignant The number of tumours which arose was proportional to the dose of urethane applied. The results of this experiment suggest that there may exist "incomplete carcinogens", in this case urethane acted as an "initiator" and croton oil as a "promoter"

Selbie and Robinson (1947) showed that the yields of papillomata produced by the transmissible Shope virus on rabbit's skin when the skin was pretreated with croton oil before the inoculation of the virus were much greater than those obtained on untreated skin. Selbie and Robinson (1948) also showed that carcinomatous transformation occurred regularly in this transmissible papillomatosis, especially in rabbits bearing papillomata for twelve months or more There was a higher incidence of carcinomatous change in papillomata arising from skin which had been treated with croton oil before inoculation

Selbie and Robinson (1947, 1948) state that, although carcinomatous transformation appears to be a natural stage in the development of this virus infection, it presents such a radical alteration in behaviour that it is difficult to see how this could be a continuous process, because indolent papillomata which have remained quiescent for long periods suddenly begin to grow rapidly and become malignant.

Summary

The papilloma at any site is a potential source of cancer, although it is least so in the skin

The multiplicity and coexistence of papilloma and carcinoma is probably due to multifocal neoplastic change in an area of tissue, and different phases of this change, varying from papilloma to malignancy, both without and with invasion, may be present either simultaneously or at different times

The stimulus to the dividing cell may be produced by direct chemical stimulation, or by a virus attack, which itself is probably a disturber of cellular biochemistry or by a simple mutation

We are grateful to Mr Geoffrey Parker, Mr E G Muir, and Mr J G Yates-Bell for permission to include their cases in this report. We wish to thank Dr Cuthbert Dukes for his kindly advice, and Dr Stretton Young and Dr M E Powell for the photomicrographs

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". Medicine is at heart a polygamist becoming wedded to as many of the sciences and practical arts as prove their worth Nor has medicine lacked for would-be mates, the most recent and vocal of these being the psychological and social sciences If these have at times seemed importunate and impatient, this may be because they feel themselves to have been left, for too long, to cool their heels in the vestibule And if at other times, they have acted shy and perhaps overly diffident, this may be because it is a source of wonder to them that they are being considered at all Moreover, as is often the case with polygamy, the first set of wives—say, the biological and chemical sciences—are reluctant at first to approve yet another burden to the menage But there is still hope As the burden of work plainly becomes more than can be managed by the present members of the household, they become ready for new accessions to help carry the load of what needs to be done"—R. K MERTON, *The Student-Physician*, p 32 Cambridge, Mass, 1957

ESSENTIAL FATTY ACIDS, LIPID METABOLISM, AND ATHEROSCLEROSIS *

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WORK done in this laboratory in 1950–52 showed that the ingestion of certain different vegetable fats, under precisely controlled conditions, was associated with a major sustained fall in the level of plasma-cholesterol and plasma-phospholipids (Kinsell et al 1952, 1953) This work has been confirmed by Ahrens et al (1955), Beveridge et al (1955, 1956), Malmros and Wigand (1955, 1957), Bronte-Stewart et al (1956) and others Clinical observations of Groen et al (1952) and Groen (1957) also have indicated significant differences between the effects of fats of animal and vegetable origin as regards plasma-cholesterol levels, possibly in relation to some of the manifestations of atherosclerosis

Our studies in 1951–55 indicate (by exclusion and by direct evidence) that the polyunsaturated fatty acids in the diet are the common factor probably responsible for these effects on plasma-lipids (Kinsell and Michaels 1955, Friskey et al 1955, Kinsell et al 1956a and b), but the following questions remain to be answered

(1) Do polyunsaturated fatty acids per se lower the plasma-cholesterol level as efficiently as do natural fats containing the same amounts of the same acids?

(2) Is linoleic acid an essential fatty acid in man, as it is in the rat? If so, are characteristic plasma-lipid patterns associated with a deficiency and an abundance of this acid in the diet?

(3) Is anything known about the way in which essential fatty acids lower the plasma-cholesterol level?

(4) Are the changes in plasma-lipid levels associated with the ingestion of fats containing linoleic acid desirable because they either prevent or improve atherosclerosis?

(5) If so, can the desired change in the plasma-lipid levels be achieved by "fortification" of mixed diets, especially those containing customary amounts of animal and dairy fats?

(6) Are diets containing large amounts of essential fatty acids better or worse than diets containing very little fat in lowering the plasma-lipid levels to prevent or to improve atherosclerosis?

(7) Are more unsaturated fatty acids than linoleic acid (e g, arachidonic acid) more effective than it in lowering the plasma-cholesterol level?

On the basis of data accumulated in this laboratory over the past three years partial or complete answers to the above questions are available

Methods

Unless otherwise indicated, all the studies reported were made in patients in the metabolic ward Nutrients were provided as homogenised mixtures and consumed hourly from 9 A M to 9 P M These formulæ were chemically constant in a precise quantitative sense and were nutritionally adequate in terms of calorie content and quantity and quality of proteins, minerals, and vitamins (including generous amounts of crude desiccated liver) Unless otherwise indicated, the only variables were fat and carbohydrate

The methods of determining most of the lipids have been described previously (Kinsell et al 1953) The quantitative chromatographic separation of plasma-cholesterol esters and the colorimetric determination of iodine values were done by the method of Michaels et al (1958)

Determinations of substances in stools and urine were done on portions of seven-day specimens

Experimental and Clinical Observations

(1) *Do polyunsaturated fatty acids per se lower the plasma-cholesterol level as efficiently as do natural fats containing the same amounts of the same acids?*

Case 1—Table I shows the findings in a man, aged 27, with familial hypercholesteræmia Between the ages of 22 and 26 he had two episodes of myocardial infarction Before admission to the metabolic ward he received amounts of safflower oil which, in more than 90% of patients studied, produced and maintained a profound fall in the plasma-cholesterol level In this patient, however, the plasma-cholesterol level did not fall (compared with values on a low-fat regimen), but the iodine value of his plasma-cholesterol fatty acids increased from less than 100 to more than 140

Treatment and progress—On admission to the metabolic ward he received initially a chemically constant and fat-free diet followed by the substitution, for calorically equivalent amounts of carbohydrate, of 40, 60, and finally 80 g of purified ethyl linoleate Consumption of the fat-free diet was associated with a fall in the plasma-cholesterol level and a decrease in

TABLE I—FINDINGS IN CASE 1 WITH FAMILIAL HYPERCHOLESTERÆMIA

Date	Diet	Plasma-cholesterol level (mg per 100 ml)	Cholesterol-ester-fatty-acid iodine value	Plasma neutral-fat (mg per 100 ml)	Plasma phospholipid level (mg per 100 ml)	Fecal sterols (g daily)	Fecal fat (g daily)
March							
25	2000-cal fat-free	375	158	496	334		
28		391	136	qns	310		
April							
1		350	117	449	284	0 72	0 9
4		347	135	375	270		
6		326	114	331	255		
8	2000-cal with ethyl linoleate 40 g	326	138	343	250	1 23	0 6
10		307	138	344	256		
11		306	150	261	290		
13		366	172	261	295		
15		341	167	291	273		
17		340	151	339	275	1 35	1 2
18		313	156	315	247		
22	2350-cal with ethyl linoleate 40 g	315	185	291	270	1·20	1·0
24		317	158	296	273		
25		325	154	258	273		
29	2450-cal with ethyl linoleate 60 g	273	156	317	241	1 56	1 3
May							
1		300	162	297	247		
2		298	155	280	255		
5		323	154	358	254	1 16	0·8
6		306	150	271	245		
8		300	156	275	247		
9		269	156	231	220		
13		262	167	373	247	1 41	0 6
15		295	142	360	270		
18		296	152	348	263		
20	2750-cal with ethyl linoleate 80 g	300	154	302	243	1 23	1 1
22		255	139	299	268		
23		267	145	303	313		
25		331	164	146	357		
26		293	139	242	257		
27		291	150	259	268		

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* Presented in part at the Gordon Conference on Lipids (June, 1957), the Fourth International Conference on Lipids (Oxford University, July, 1957), and the International Congress on Nutrition (Paris, July, 1957) This work has been supported in part by grants from the Schering Corporation, the Armour Laboratories, the Borden Company, the Upjohn Company, the Alameda County Heart Association, and the National Institute of Health Grateful acknowledgment is made to members of the research staffs of the Armour Laboratories, the Pacific Vegetable Oil Company, and Procter and Gamble for supplies of lipid materials used in these studies, to Merck and Company for supplies of digitonin, to the Borden Company for supplies of 'Borden Instant Coffee', to the Nestle Company, Inc for 'Nestea', and to Mead Johnson and Company for 'Casec' used in the balance studies

the cholesterol-ester-fatty-acid iodine value The addition of ethyl linoleate to the diet was associated with a further fall in the plasma-cholesterol level and an immediate increase in the cholesterol-ester-fatty-acid iodine value

It can be concluded from the evidence presented in this patient and in a healthy boy (table II) that question 1 is answered in the affirmative

(2) *Is linoleic acid an " essential " fatty acid in man, as it is in the rat? If so, are characteristic plasma-lipid patterns associated with a deficiency and an abundance of this acid in the diet?*

Table II shows the findings in case 2, a healthy boy, aged 19, who was in hospital with a fractured femur It is apparent that, compared with the fat-free diet, the addition of ethyl linoleate to the diet produced a profound fall in the fasting plasma-cholesterol, neutral-fat, and phospholipid levels and an increase in net unsaturation of cholesterol-ester-fatty acids to values well in excess of the administered material When oleate was substituted for linoleate, the plasma-cholesterol, neutral-fat, and phospholipid levels slowly rose after an initial "lag period", and the iodine value decreased rapidly The " lag period " associated with the initial administration of oleic acid was probably related to the availability of essential fatty acids from depots as the result of previous administration of linoleate as well as to contamination of the oleate with linoleate and linolenate (1–6% in different preparations)

These results in this healthy boy supply affirmative answers to the questions raised in item 2 Further studies will be required to substantiate this conclusion and are under way

We cannot explain the increased fæcal excretion of sterols noted during feeding with oleate No such effect was noted in case 6 (table V) Additional studies now in progress may clarify this finding Other linoleate data are contained in table V

TABLE II—FINDINGS IN A HEALTHY BOY AGED 19

Date	Diet	Plasma cholesterol level (mg per 100 ml)	Cholesterol ester-fatty acid iodine value	Plasma neutral fat (mg per 100 ml)	Plasma phospholipid level (mg per 100 ml)	Fæcal sterols (g daily)	Fæcal fat (g daily)
May							
16	2500-cal. fat-free	153	158	219	181		*
17		166	166	196	178		
18		171	131	212	210		
19		160	122	229	189		
20		150	149	274	189	0 76	1 1
22		118	150	262	178		
23		105	147	365	211		
27		140	148	535	258		
29		135	141	405	220		
30		132	135	398	206	0 37	0 9
June							
3		141	120	426	215		
5		150	117	351	208	1-01	0 8
6		145	108	338	218		
10	Ethyl linoleate 80 g added	148	118	375	213		
12		148	201	229	188	0-62	7 1
13		105	211	180	183		
17		90	180	219	131		
19		76	175	267	122	0-67	2 7
20		78	259	202	103		
22		69	275	219	140		
24	Ethyl oleate 80 g added	95	248	217	125		
26		100	159	201	138	1 43	3 1
27		78	173	233	125		
29		79	163	232	161		
July							
1		103	108	317	156		
3		115	168	347	163	1 87	1-9
4		117	164	337	189		
5		115	167	265	167		
8		133	135	322	181		
10		130	135	302	181		
11		117	143	303	188	1-60	0 79
15		122	144	282	200		
17		126	152	251	169		
18		123	158	236	181		

TABLE III—FINDINGS IN CASE 4

Date	Diet	Plasma-cholesterol level (mg per 100 ml)	Cholesterol-ester-fatty-acid iodine value	Plasma-neutral fat (mg per 100 ml)	Plasma-phospholipid level (mg per 100 ml)	Fæcal sterols (g daily)	Fæcal fat (g daily)
Jan							
21	2000-cal with 200 g lard	165	131	148	187	—	10·0
23		140	—	181	160		
25		145	—	186	168		
28		175	109	147	206		
Feb							
1		173	—	160	194	—	6 8
4		163	143	201	166		
8		156	99	216	178	0 95	12 88
11	150 g lard, 50 g safflower oil	159	109	228	175	0 78	8 59
15		151	—	218	175		
18		148	127	235	181	0 61	9·09
22		164	—	269	175		
25		179	—	199	170	0 71	8 4
28		168	—	160	169		
March							
1		178	—	159	168		
4	100 g lard, 100 g safflower oil	184	144	164	181	0 74	8 8
8		140	—	228	160		
11		150	148	177	160		
15		158	—	179	160	0 36	9 6
18		140	—	203	153		
21		134	—	235	153	0 91	10 2
25		135	136	232	169		
28		125	185	211	150	1 15	21 1
April							
1	50 g lard, 150 g safflower oil	113	179	—	—	1·01	15 6
4		130	130	220	144		
8		132	—	227	140	1·47	13 2
11		145	—	173	175		
15		154	199	203	156	2·07	16 9
18		153	150	233	162		
22	200 g safflower oil	147	187	250	162	1 11	7·4
25		149	—	213	172		
29		128	166	232	163		

(3) *Is anything known about the way in which essential fatty acids lower the plasma-cholesterol level?*

No A working hypothesis which is not incompatible with available data and which is susceptible to systematic experimental assessment is considered below

(4) *Are the changes in plasma-lipid levels associated with the ingestion of fats containing linoleic acid desirable because they either prevent or improve atherosclerosis?*

No answer which applies with certainty to the population at large is available, nor will it be for some time On the basis of certain observations, however, a provisional answer may be at hand In the past three years more than 80 outpatients with known vascular disease were observed before and during the consumption of diets containing large amounts of fats rich in linoleic acid

The fats used included cotton-seed, soy, corn, walnut, peanut, and safflower oil At present safflower oil is being used almost exclusively because it contains more linoleic acid than does any other fat which is readily available commercially (70–80% in most lots) According to the caloric requirement and clinical status of the patient 40–180 g daily of such fats was included in the diet The precise make-up of these diets is being reported by Olson and Kinsell (1957)

Many of the same problems which apply to the management of diabetics apply to dietary regulation of this group of patients None of these problems is insurmountable For any patient to be admitted to a semi-controlled clinical programme designed to provide interpretable answers, certain basic requirements are necessary in the patient integrity, adequate intelligence, and willing cooperation There must be adequate personnel and facilities for group and individual instruction, periodic clinical assessment, dietary supervision, and precise laboratory follow-up

Patients observed in the ambulatory group included those who had had one or more coronary occlusions, those with cerebral vascular disease, those with various forms of xanthomatosis, and those aged less than 50 with peripheral vascular disease

The only statement we are prepared to make about the coronary group (more than 50 patients, some of whom have been followed up more than three years) is that all the patients "feel better" who have kept to the diet rich in essential fatty acids and no patient has had a new coronary occlusion while taking a diet rich in vegetable fat Most of these patients had been on a low-fat diet before the study In view of the opinion prevailing in most quarters before 1956 that "fats were bad" regardless of the nature of the fat, we had some trepidation about giving these patients high-fat diets Hence the absence of clinical evidence of progressing disease has been gratifying If such freedom from new coronary occlusion continues for a significant time one may be entitled to draw conclusions, but hitherto the study has been too short and the patients have been too few

Several of the patients with cerebral vascular insufficiency feel better on a diet rich in essential fatty acids, but there is no adequate way of assessing this statement at present

As regards the patients with peripheral vascular disease, we have reason to believe that something desirable has happened in association with the high intake of essential fatty acids, but oscillometric readings are notoriously unreliable, and it is well recognised that relative vascular insufficiency in the legs fluctuates as regards functional capacity However, when functional improvement is consistently associated with a specific programme, there may be reason to believe that it is more than coincidental

Case 3—A *man*, aged 47, was referred for assessment in September, 1956, with severe pain and cramping in his legs, and angina pectoris on slight exertion He had had two myocardial infarctions His weight was normal for his height and age and has remained so Pulsation was absent bilaterally from his dorsalis pedis and posterior tibial arteries

Treatment and Progress—On Sept 20, 1956, he was changed from the low-fat 1800-calorie diet which he had taken for a long time, with progressive deterioration of his clinical status, to an 1800-calorie diet containing about 135 g of cottonseed or of safflower oil daily (Olson and Kinsell 1957) On this he continued until March 2, 1957 By Oct 18 walking was less of an effort, but he still had much angina By Jan 10, 1957, he could "walk indefinitely" (compared with the length of three city blocks in October, 1956) On Feb 2, he stated that he had walked twenty blocks without effort, and that he was free from chest pain On March 2 he had returned to the full activity as a "trouble-shooter" for the telephone company (after two and a half years' disability sufficient to prevent him from participating in anything except office work) On this date he was changed to an 1800-calorie diet containing about 70 g of fat including more than 35 g of *linoleic acid* In mid-April questionable pulsations were felt in his right posterior tibial artery On June 22 pulsations were strongly palpable in both posterior tibial arteries, and questionable pulsation was noted in his right dorsalis pedis artery

TABLE IV—FINDINGS IN CASE 3

Date		Diet	Plasma cholesterol level (*mg per* 100 ml)	Plasma-neutral-fat level (*mg per* 100 ml)	Plasma-phospholipid level (*mg per* 100 ml)
Oct	19	1600-cal	170	317	209
,,	21	100 g coconut oil	183	173	202
,,	24		200	108	203
,,	26		164	221	195
,,	28		165	316	206
,,	31		154	233	213
Nov	2		183	209	213
,,	4		172	335	194
,,	7		163	172	181
,,	9	80 g coconut oil	173	155	203
,,	11	20 g soy	178	156	195
,,	14		169	198	213
,,	16		179	—	218
,,	18		170	—	181
,,	21		173	—	188
,,	23		175	—	191
,,	25		151	—	188
,,	28	50 g coconut oil	150	—	183
,,	30	50 g soy	143	166	175
Dec	2		143	165	156
,,	5		125	195	156
,,	7		117	214	154
,,	9	20 g coconut oil	103	167	144
,,	12	80 g soy	94	166	125
,,	14	100 g coconut oil	109	291	147
,,	16		109	325	169
,,	19		136	—	—
,,	21		161	213	172
,,	23		174	145	180

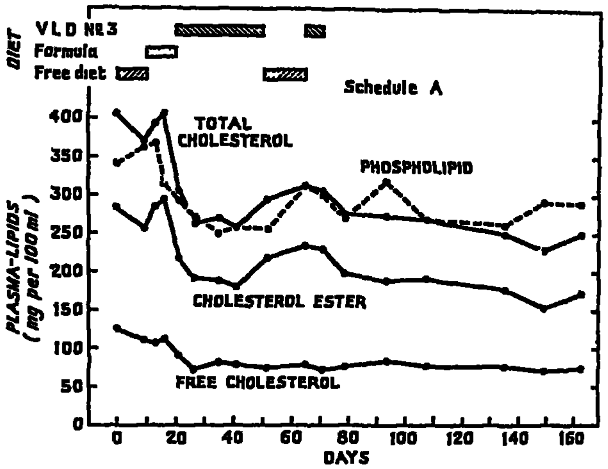

Fig 1—Semi-controlled study in an ambulant patient The formula and Schedule A diets and vegetable lipid diet no 3 all contained more than 35 g of linoleic acid daily and little animal fat These diets are described by Olson and Kinsell (1957)

Of the other patients with peripheral vascular disease several have shown equally good symptomatic and functional improvement None has yet shown return of palpable pulsation in vessels in which, before the diet rich in essential fatty acid, no pulsation was felt

All of those who have responded have shown the usual considerable sustained fall in plasma-cholesterol level In some this has been associated with a decrease in the cholesterol/phospholipid ratio Studies of fatty-acid composition of the plasma-cholesterol esters have not been possible until recently in this group

All this is consistent with an affirmative answer to question 4 Further observation is obviously required

(5) *If the answer to question 4 is in the affirmative, can the desired change in the plasma-lipid levels be achieved by "fortification" of mixed diets, especially those containing customary amounts of animal and dairy fats?*

It may be well to consider certain precisely controlled metabolic studies in which mixtures of vegetable and animal fat are used Table III illustrates such a study

Case 4—A man with mild diabetes received a chemically constant diet containing 200 g of fat daily He was free from demonstrable vascular disease and had a low plasma-cholesterol level on any diet given him When lard comprised the only source of fat, or when 50 g of safflower oil was substituted for an equal amount of lard, the cholesterol levels remained practically constant The safflower oil used in this study contained 73% of linoleic acid Increase of the safflower oil to 100 g instead of an equal amount of lard led to a prompt and major fall in the plasma-cholesterol level The averages for cholesterol-ester-fatty-acid iodine values were significantly greater during this period

Table IV shows the finding in a woman aged 49, with no evidence of vascular disease, in whom coconut oil was "titrated" against soya oil As with lard and safflower oil, a 50% substitution of soy for coconut was required to obtain a major fall in plasma-cholesterol level The coconut oil contained practically 100% saturated acids, and the soy oil contained about 50% linoleic acid and some linolenic acid

Fig 1 shows the findings in an ambulant male outpatient, aged 58, with hypercholesterolæmia, xanthelasma, and clinical evidence compatible with probable generalised asymptomatic atherosclerosis During the course of formula and mixed diets, which contained two or more parts of highly unsaturated fat to one portion of predominately saturated fat, a very significant and maintained fall in the plasma-cholesterol level was observed in this extremely cooperative patient

Observations during the last four years indicate that young healthy adults require a quite small proportion of linoleic acid to the sum of saturated fatty acid and fatty-acid precursor to maintain a relatively low plasma-cholesterol level The greater the amount of vascular disease, the larger is the amount of essential fatty acids required to lower the plasma-cholesterol level It seems not unreasonable to relate this observation to impairment of efficiency to conserve and/or utilise essential fatty acid in the abnormal individuals Whatever the reasons, it seems probable that 10 g of linoleic acid in a young healthy person is sufficient to keep the plasma cholesterol and phospholipid levels below 170 mg per 100 ml, if the dietary intake is otherwise "average" Very abnormal patients—e g, some with xanthomatosis—may require more than 50 g of linoleate daily in association with a relatively low intake of saturated fatty acid and precursor thereof

Approximate requirements in three groups are shown diagrammatically in fig 2 In patients with known vascular disease who initially respond poorly to the mixed diet, it is our custom to limit the intake of food to a formula diet plus supplemental vitamins for one to four months, or until the cholesterol level has reached and been maintained at a normal level for more than a month The greater efficiency of the mixed diet after such "loading" may be referable to relatively high concentration of polyunsaturated fatty acids in the fat depots as well as to possible improvement in the efficiency of conservation and utilisation of essential fatty acids

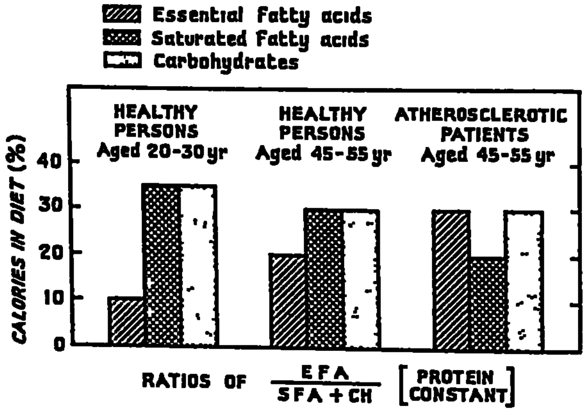

Fig 2—Approximate requirements of essential fatty acids in relation to age and pathology This is a rough approximation subject to later correction The diets used in the studies on which these approximations are based contained more than average amounts of protein

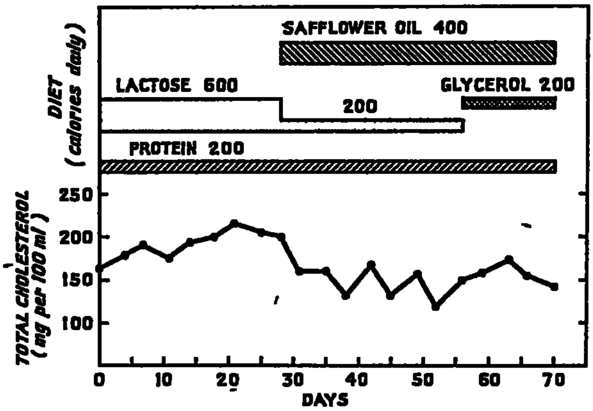

Fig 3—On fat-free 800-cal diet plasma-cholesterol level rose Substitution of 44 g of ethyl esters of safflower fatty acids for calorically equivalent amount of carbohydrate was associated with progressive fall of the plasma-cholesterol level Patient was in nitrogen equilibrium throughout

To summarise, it appears that the inclusion of adequate amounts of natural fats containing 40–80% of linoleic acid in mixed diets will lower the plasma lipid levels The actual amount of linoleic acid required depends on the composition of the diet and the clinical status of the patient

(6) *Are diets containing large amounts of essential fatty acids better or worse than diets containing very little fat in lowering the plasma-lipid levels to prevent or to improve atherosclerosis?*

For the reasons noted above it is extremely difficult to assess the clinical efficacy of any diet Our only comment would be that all the patients with partially occlusive vascular disease who improved clinically on a diet containing plenty of linoleic acid had for a long time been taking diets containing extremely little fat On these diets, in the opinion of the patients and their physicians, their course had been progressively downhill

As regards the virtues of a low-fat diet in terms of plasma-cholesterol level, the answer is very much more easily obtained A low-fat diet is, of necessity, a high-carbohydrate diet Fig 3 shows a portion of a study in an obese female with no evidence of vascular disease While she was receiving a fat-free low-calorie diet the plasma-cholesterol level rose progressively When 100 g of carbohydrate was replaced by a calorically equivalent quantity of the ethyl esters of fatty acids derived from safflower oil, there was a highly significant fall in the plasma-cholesterol level and this was maintained

The findings in a healthy control (table II) also emphasise the remarkable qualitative and quantitative differences in the plasma lipids during the intake of a "no-fat diet", compared with a dietary including large amounts of essential fatty acids

From these studies it appears that diets rich in essential fatty acids are much more effective in lowering plasma-lipid levels than are very low-fat (high-carbohydrate) diets Time and further work will provide additional information on the relationship of such diets to atherogenesis

(7) *Are more unsaturated fatty acids than linoleic acid (e g, arachidonic acid) more effective than it in lowering the plasma-cholesterol level?*

An approach to an answer to this question has been most difficult because of the unavailability of purified arachidonic-acid preparations

Table v shows some findings in a hypercholesterolæmic patient with xanthomatosis and mild diabetes Administration of a phosphatide mixture derived from mammalian liver, with a fatty-acid composition of 12 5% of tetranoic (probably cis-arachidonic) acid, saturated acids 75%, oleic acid 5%, and conjugated dienes 2 4%, was associated with a profound fall in the plasma-cholesterol level, compared with the level on a diet in which all of the fat was derived from coconut oil Very large amounts of purified ethyl linoleate and trilinolein did not lower the plasma-cholesterol level so much When oleate was substituted for linoleate, the iodine value of the cholesterol-ester fatty acids decreased promptly, and after an initial lag period the plasma-cholesterol level progressively rose to the values observed with coconut oil The reasons for the lag period are probably identical with those noted in the healthy young male (table II)

This study is compatible with the concept that arachidonic acid may be a much more potent hypocholesterolæmic agent than linoleic acid (see below)

TABLE V—FINDINGS IN PATIENT WITH XANTHELASMA AND DIABETES

Date	Diet	Plasma-cholesterol level (mg per 100 ml)	Cholesterol-ester-fatty-acid iodine value	Plasma-neutral fat (mg per 100 ml)	Plasma-phospholipid level (mg per 100 ml)	Fæcal sterols (g daily)	Fæcal fat (g daily)
March							
11	1850-cal 75 g coconut oil	311	—	246	320	0 58	3 2
15		313	—	362	316		
18		288	129	341	310	0 49	2 2
21		330	—	372	347		
25		276	118	qns	313	0 19	1 9
28		313	—	428	306		
April							
1	75 g arachidophosphatides	318	126	367	328	2 12	13 4
4		240	156	329	260		
6		235	194	302	257		
8		234	153	318	260	2 72	14·4
10		210	150	358	282		
11		206	164	304	257		
13		240	170	249	281		
15		240	154	277	263		
17		233	178	340	265	2 16	11 4
18		235	176	293	269		
22	37 5 g arachidophosphatides, 37 5 g coconut oil	240	184	309	256	1 92	9 7
25		273	183	285	280		
29		242	194	318	278		
May							
1		255	186	347	300	2 04	11 9
2		267	—	349	294		
6	37 5 g coconut oil, 37 5 g ethyl linoleate	305	171	305	306	0 54	1 3
8		283	173	314	283		
9		257	173	226	263		
13		270	—	260	269	0 52	1 1
15		287	159	331	300		
16		262	150	282	343		
20	25 g coconut oil 50 g ethyl linoleate	319	142	303	288	0 65	2 4
22		270	154	349	323		
23		270	144	268	285		
27	25 g coconut oil 50 g trilinolein	260	130	286	285	0 43	1 1
29		265	146	287	269		
30		265	156	264	256		
June							
3		281	150	273	256		
5	75 g trilinolein	280	169	345	300	0 83	1 5
6		301	173	229	298		
8		263	197	257	281		
10		260	184	268	255		
12		270	181	220	258		
13	75 g triolein	260	184	241	255	0 41	1 6
15		252	170	320	256		
17		232	170	300	269		
19		237	142	338	275		
20		235	128	320	258	0 56	0 8
24		240	125	315	269		
26		235	119	213	263		
27	75 g ethyl oleate	258	135	347	267		
29		247	109	334	288		
July							
1		253	134	294	294		
3		253	129	371	356	0·97	1 3
4		266	130	346	300		
5		280	118	368	302		
8		275	138	327	269		
10		305	126	339	295	0 56	2 75
11		300	122	313	319		
15		293	132	372	317		
17		322	qns	qns	298		
18		297	143	165	245		

Discussion

There appears to be no question but that a high intake of polyunsaturated fatty acid can produce a major fall in plasma-cholesterol level and a net increase in unsaturation of the cholesterol-ester-fatty acids Comparable qualitative and quantitative changes in the plasma-lipids do not result from the intake of a low-fat or a fat-free diet, from a diet containing oleic acid as a source of unsaturated fatty acid, or under any other conditions of which we are aware This by no means excludes the concept that factors in vegetable fats other than the polyunsaturated fatty acids have some significant effect on plasma-cholesterol levels Beveridge et al (1955, 1956) have excellent evidence that the addition of β-sitosterol to a low-fat diet will lower the plasma-cholesterol level They feel that there is possibly some synergistic relationship between certain of the vegetable sterols and the polyunsaturated fatty acids

Other investigators suggest the possibility that unknown materials present in trace amount in natural fats may be responsible for lowering the plasma-cholesterol level Such a hypothesis seems unnecessary in view of the evidence presented here

Keys et al (1957), on the basis of somewhat unconvincing data, and Ahrens et al (1957), from observations with natural fats containing considerable quantities of oleic acid, have advanced the hypothesis that double bonds furnished by fatty acids are responsible for the effects observed—i e , sufficient oleate would be quite as effective as linoleate or arachidonate Our studies do not support such a hypothesis

In view of the ease with which oleate can be formed from carbohydrate and other entities, such a hypothesis would not seem tenable in any event Mead's (1957) studies indicate that oleic acid is metabolised quite differently from linoleic acid One may anticipate that this picture will come into much sharper focus within the next year It is our impression, however, that the amount of linoleic acid required to " balance " a given amount of oleic acid may be less than that required for an identical amount of stearic or of palmitic acid Work designed to assess this statement further is in progress

Earlier in this paper the question was raised " Is information available about the *mechanism of depression* of the plasma-cholesterol level by essential fatty acids ? " Increased excretion of cholesterol might conceivably be an explanation This seems *unlikely to us (at least as* an explanation of the major portion of the effect) for the following reasons

(1) It subscribes to the long-standing, perhaps naïve, philosophy that cholesterol is " bad " and must be exorcised

(2) The excretion pattern observed in different people is unpredictable and bears no necessary *relationship to* the changes in blood levels

More probably, the effect of essential fatty acids is by regulating the production of cholesterol A final explanation has not yet been found, but the following is a working hypothesis which has been changed but little since 1955

Since the reports of Stetten and Boxer (1944) and Stetten and Klein (1945) many other reports have been published supporting the concept that fat is the " prime fuel " of the body This is probably so, regardless of the dietary intake A low-fat diet inevitably is a high-carbohydrate diet Under most conditions the greater portion of ingested carbohydrate is probably transformed to fatty acids in the fat depots and eventually mobilised and metabolised through fatty-acid pathways Conse-

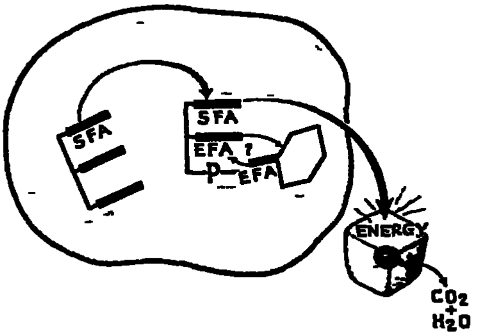

Fig 4—Transport of fatty acids glycerids carry bulk of fuel fatty acids, lecithin is the most metabolically active transporter of fuel fatty acids, turnover of saturated fatty acids (S F.A) is much more rapid than the turnover of remainder of lecithin molecule

quently two major problems exist—how fatty acids are transported and how they are rendered soluble

In round figures, a 6-ft man indulging in normal activity transports and utilises about 1 mol of fatty acid, nearly 300 g (computed as C_{18} acid) in twenty-four hours After a meal the plasma-lipid level in healthy people is higher than 700 mg per 100 ml Of this total lipid about 60% is fatty acid (glyceride, phospholipid, &c) Because of the very limited aqueous solubility of most of these lipids and the toxicity of those compounds which are somewhat soluble (e g , sodium oleate and certain mono- and di-glycerides) protein adsorption of lipids becomes an overwhelming necessity A series of " lipoproteins " exists, ranging from the high-density small-molecule albumen-fatty-acid complex (almost entirely protein) through the α and β lipoproteins to the low-density large-molecule chylomicrons (almost entirely fat, just enough protein to prevent coalescence of fat-droplets and consequent embolism) None of the foregoing sheds any light on the need for essential fatty acids

In healthy people the fatty acids which make up the plasma neutral fats are predominantly saturated and mono-unsaturated The most abundant plasma-phospholipid lecithin contains one non-essential and one essential fatty acids (Deuel 1951) The fatty acids esterified with cholesterol are predominantly unsaturated under normal conditions (Kelsey and Longenecker 1941) As shown in fig 4, we conceive of triglyceride as the donator of " fuel " fatty acid, phospholipid as the most metabolically active transporter of fuel fatty acid, " cholesterol ester " as a donator of essential fatty acid for new phospholipid synthesis, and essential fatty acid as a most important part of the phospholipid molecule, perhaps in terms of " key-in-lock " enzymatic specificity Under usual conditions the turnover of the non-essential fatty-acid portion of the phospholipid is extremely rapid, the turnover of the remainder of the lecithin molecule is quite slow Normally, therefore, the same molecule of essential fatty acid is conserved and re-utilised many times

If this theory is correct, the mechanism of lowering of the plasma-cholesterol level by essential fatty acid may be by way of decreased synthesis of cholesterol as the result of increased efficiency of the systems involved The results of some experiments on animals are in accord with this interpretation (Wood and Migicovsky 1956) Conversely, in the presence of a deficiency of essential fatty acid there may be increased production of cholesterol and phospholipic, raised levels thereof in the plasma, and increased tendency to their abnormal deposition We again emphasise that this is an oversimplified working hypothesis which undoubtedly will undergo modification as further knowledge accumulates The fact that, for the present, it neglects the role of essential fatty acids in cellular structure in no way implies that this aspect of the biochemistry of essential fatty acids is not of tremendous importance

There is no possible substitute for long-term clinical and chemical observation to determine whether diets relatively or absolutely rich in essential fatty acids have major value in the prevention or the treatment of atherosclerosis We have noted the available evidence which indicates that such diets are not harmful and may, in some people, produce desirable effects If further observations are in agreement, the concepts advanced by Sinclair (1956) regarding the pathogenesis of atherosclerosis will deserve most serious consideration, with particular reference to the role of food processing If it is possible to improve existing vascular disease by diet, much lesser dietary modification should have significant prophylactic value In support of this concept one notes the smaller proportion of dietary linoleic acid to saturated fat and saturated fat precursors required to lower the plasma-cholesterol level in healthy young people

Summary

The addition of purified ethyl and glycerol esters of linoleic acid to the diet lowers the plasma-lipid levels in healthy and in unhealthy people The addition of oleic-acid preparations does not do this

On the basis of these and earlier observations it can be concluded that the major active ingredient in various vegetable fats responsible for lowering the plasma cholesterol is linoleic acid

Results obtained with a phosphatide mixture containing arachidonic acid suggest that this acid may be much more potent, gramme for gramme, in lowering the plasma-cholesterol level than is linoleic acid, at least under the conditions noted

There is some evidence that palatable mixed diets rich in essential fatty acids, in addition to lowering the plasma-cholesterol level, are also associated with clinical improvement in patients with arterial degenerative disease

Evidence is presented that the prescription of a low-fat diet is biologically unsound

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PENTACYNIUM BIS-METHYLSULPHATE (PRESIDAL) IN THE MANAGEMENT OF HYPERTENSION

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Locket (1956) reported preliminary results obtained with two members of a group of ganglion-blocking agents in which there was an apparent dissociation between hypotensive activity and the ability to produce ocular changes and gastrointestinal disturbances The most active member was 139 C 55, pentacynium or ‘Presidal’, and this paper describes a clinical study of this compound given by injection and orally to a series of 30 severely hypertensive patients for periods of from three to eighteen months

Presidal is N^1-(5-cyano-5-5-diphenylpentyl)-N^1 N^1 N^2 trimethylethylene-1-ammonium-2-morpholiniumbis-methylsulphate, a member of a series of unsymmetrical bisonium salts first described by Adamson et al (1956), its structural formula is shown in fig 1 The chemistry of this compound and its close analogues has been described by Billinghurst (1956), and its pharmacology has been reported by Green (1956)

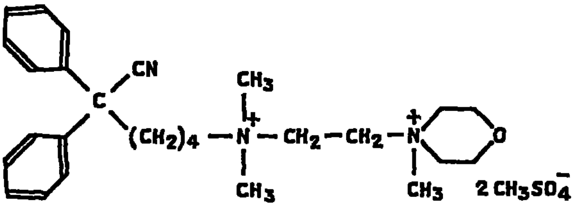

Fig 1—Structural formula of pentacynium bis-methylsulphate.

Material and Method

Selection of Cases

The group of patients studied comprised 30 consecutive admissions for severe hypertension to the wards of the Liverpool Regional Cardiac Centre The criteria for selection were (1) malignant hypertension with papillœdema, and (2) essential hypertension severe enough to produce incapacitating symptoms or serious cardiac or cerebral complications

17 of the patients were men and 13 women Their ages ranged from 41 to 68 with a mean of 55 The length of history of hypertensive symptoms varied from two weeks to ten years On the Keith et al (1939) classification of the severity of hypertensive disease based on fundal changes, 6 fell into group IV, 8 into group III, and the remainder into group II Gross dyspnœa was present in 19, and 28 of the 30 patients had electrocardiographic evidence of myocardial disease or severe left-ventricular strain 5 had already had an attack of myocardial infarction, and 8 had had a cerebral thrombosis or subarachnoid hæmorrhage

Method

On admission the hypertension was fully investigated and the patient's cardiac, renal, and cerebral condition assessed A test dose of pentacynium was then given by subcutaneous injection, and blood-pressure readings were taken over a period of twelve hours To maintain uniformity throughout this series and to make possible comparison with other series, the blood-pressure was measured by the method recommended by the Committee for the Standardisation of Blood Pressure Readings (1939)

Oral therapy was then begun, the initial daily dose and its distribution depending on the extent and duration of the blood-pressure fall obtained with the test dose The dose was gradually increased until stabilisation was obtained In 13 instances reserpine 0 25 mg t d s was added to the treatment After stabilisation the patient was discharged and followed up monthly in the outpatient clinic

Results

Blood-pressure Response to a Single Dose

All patients except 1 showed a significant fall in the supine systolic and diastolic blood-pressures when given a subcutaneous test-dose of pentacynium, which ranged from 3 to 10 mg The degree of blood-pressure fall varied with the dose given 10 mg produced a mean systolic fall of 90 mm Hg and a diastolic fall of 40 mm in the supine position, 3 mg produced a mean systolic fall of 70 mm and a mean diastolic fall of 30 mm The blood-pressure started to fall on an average ten minutes after injection and reached its lowest level after one to one and a half hours It remained at this level for several hours and then rose slowly to its initial height in six to twenty-four hours, with a mean of twelve hours In the standing position there was greater hypotension, and in the trough of the blood-pressure fall hypotensive symptoms were often present A typical blood-pressure response after a test dose of pentacynium is shown in fig 2

Intravenous administration produced a greater and more rapid fall of blood-pressure than did subcutaneous or intramuscular injection The action began within five minutes, and the trough of the blood-pressure fall was reached in fifteen to twenty minutes After oral administration, the blood-pressure began to fall after twenty to thirty minutes and the effect was greatest about an hour later After both oral and parenteral administration, the greater the blood-pressure fall the longer was its duration Postural hypotension sometimes persisted for some hours after the pressures in the supine position had returned to control levels

In most cases there was moderate slowing of the heart-rate The reduction was generally about ten to fifteen beats a minute, and this effect coincided closely with the hypotensive effect of the drug (fig 3) Pentacynium also

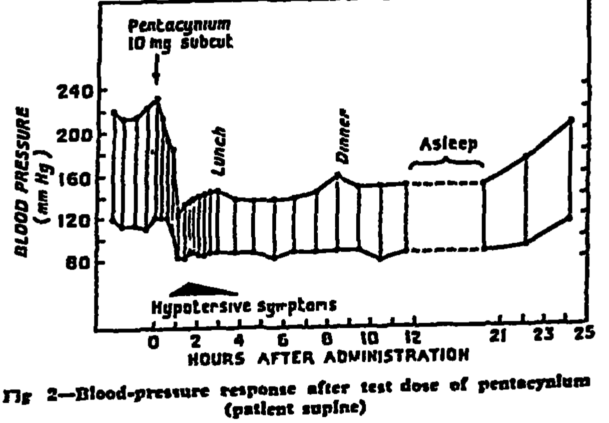

Fig 2—Blood-pressure response after test dose of pentacynium (patient supine)

inhibited the homœostatic vasoconstrictor impulses and abolished or greatly reduced the blood-pressure overshoot which normally follows the Valsalva manœuvre

Relative Potency of Parenteral and Oral Pentacynium and Other Ganglion-blocking Agents

The potency of the parenteral and oral forms was compared in 28 patients The effective oral dose was from ten to twenty times the effective subcutaneous dose, and this ratio varied from patient to patient, depending mainly on the time-relationship between administration of the oral dose and the main meals of the day

Parenterally, pentacynium was found to be about equipotent with chlorisondamine and mecamylamine, and two to three times as potent as pentolinium Orally, it was as potent as chlorisondamine, twice as potent as pentolinium and about a tenth as potent as mecamylamine

Factors Influencing Hypotensive Action

The fall in blood-pressure after pentacynium, like that after other ganglion-blocking agents, was greatest when standing, least when lying, and intermediate when sitting In 5 of the 30 patients there was an excessive postural fall, particularly during the period of stabilisation The effect of posture on the blood-pressure levels is shown in fig 3 As with hexamethonium (Smirk and Alstad 1951), pentolinium (Smirk 1953), chlorisondamine (Smirk and Hamilton 1956), and mecamylamine (Smirk and McQueen 1957), a meal taken during the course of action of pentacynium produced an additional fall in blood-pressure This postprandial fall was generally 20–40 mm Hg systolic, it began within an hour of the meal and lasted up to two hours This effect is shown in figs 2 and 3 However, in no instance was the postprandial fall greater than the post-injection fall of blood-pressure Vasodilatation due to alcohol or an increase in room-temperature also increased the hypotensive effect, as with other ganglion-blocking agents

TABLE I—MEAN AND RANGE OF BLOOD-PRESSURE FALL WITH A DOSE OF PENTACYNIUM IN PATIENTS WHO HAD PREVIOUSLY RECEIVED PENTOLINIUM, MECAMYLAMINE, OR NO TREATMENT

Previous treatment	Dose of pentacynium (mg)	No of cases	B.P fall (mm Hg)	
			Mean	Range
None	10	11	85/35	35/20–150/70
Pentolinium	10	5	100/45	85/35–120/60
Mecamylamine	10	4	85/35	60/10–100/50

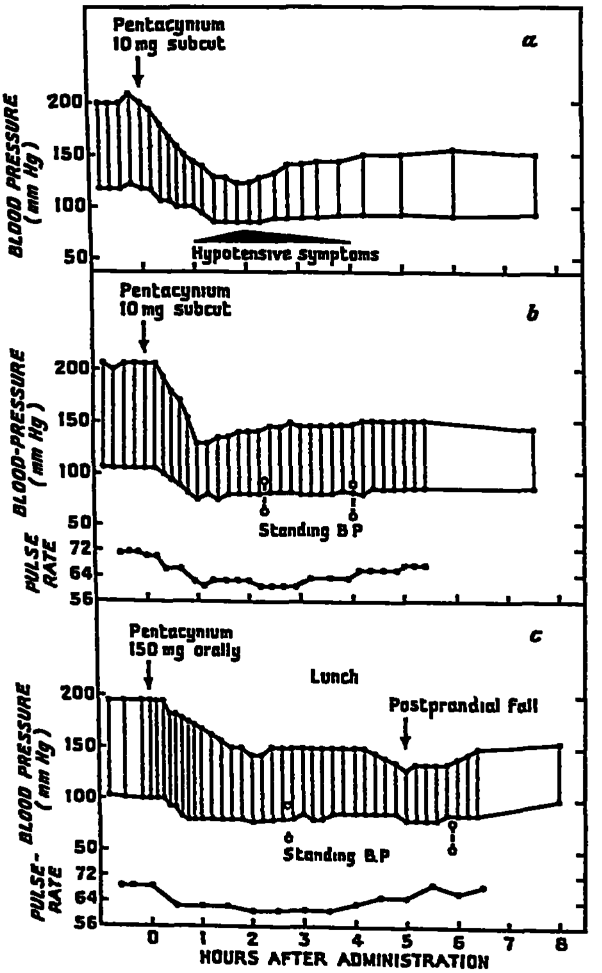

Fig 3—Blood-pressure response to pentacynium (a) test dose of 10 mg (b) test dose of 10 mg after 9 months treatment, (c) oral dose of 150 mg on empty stomach.

Tolerance and Cross-tolerance

In the first few days of treatment tolerance developed in 13 of the 30 patients To produce a similar fall of blood-pressure on consecutive days, the dose had to be increased by 10–20% In the remainder there was little evidence of tolerance, and the fall in blood-pressure obtained by repeating the test dose after many months was similar in extent and duration to that produced by the initial test dose (see fig 3)

After stabilisation it was rarely necessary to increase or decrease the total daily dose, but change in the patient's occupation or daily routine, or in the weather, sometimes necessitated alterations in the distribution of the daily dose

Cross-tolerance between pentacynium and other ganglion-blocking agents was not evident in this study No significant difference was found in the mean fall in blood-pressure after a constant dose of pentacynium between the previously untreated group and those who had been treated with pentolinium or mecamylamine (table I) A minor degree of cross-tolerance could not be excluded, however, for there was in most cases an interval of a week or more between the cessation of therapy and the administration of a test dose of pentacynium

Results of Long-term Oral Therapy

30 patients were treated by mouth for periods of from three to eighteen months The initial oral dose given was generally 50 mg three times daily, and this was increased by 25 mg every two days until an adequate response was obtained or until side-effects—generally blurred vision or postural hypotension—prevented further increase Response to treatment was classified according to the average supine diastolic pressure If this was maintained at less than 110 mm Hg, the patient was regarded as a responder, and, if not, a non-responder On this basis 24 were classified as responders at the time of assessment, and 6 as non-responders (table II) A typical response to long-term therapy is shown in fig 4

TABLE II—MEAN BLOOD-PRESSURES BEFORE AND DURING TREATMENT WITH PENTACYNIUM IN RESPONDERS AND NON-RESPONDERS

Group	No of cases	Pretreatment B P (supine)	B.P levels during treatment	
			Supine	Standing
Responders	24	235/135	165/95	140/90
Non responders	6	255/140	230/130	225/135

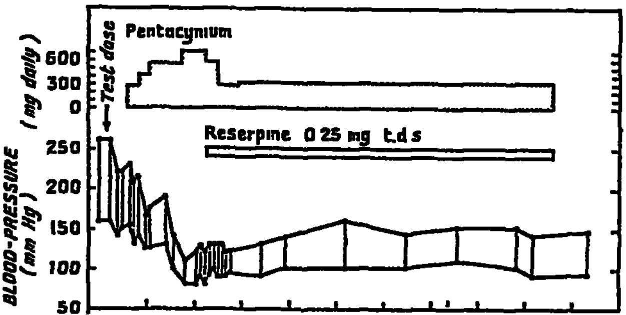

Fig 4—Blood-pressure response to long-term oral pentacynium and reserpine (0.25 mg t d s) therapy

In the group of responders the total daily oral requirement of pentacynium varied from 300 to 700 mg (mean 375 mg) This was generally given as three doses, before breakfast (7 A M), before tea (3 P M), and before retiring (9 P M) In some cases twice-daily administration was found to be sufficient, and in 1 case four doses daily were necessary Absorption was best on an empty stomach, and for this reason the before-breakfast requirement was often smaller than the afternoon and evening doses

After discharge most patients were encouraged to return to work as soon as possible and were instructed to keep rigidly to their scheme of treatment After a few weeks some patients knew without recourse to blood-pressure readings whether their hypertension was still under control, and some were able to suggest useful improvements to their daily regimen of treatment

Relief of Symptoms and Regression of Signs

Such symptoms as breathlessness on exertion, headaches, nausea and vomiting, and angina were rapidly relieved as the blood-pressure was lowered, and in most cases there was obvious regression of the signs of hypertensive disease

Where congestive heart-failure was present before treatment, this improved The heart size was often reduced and the clinical and electrocardiographic evidence of left ventricular strain became less

Retinal hæmorrhage and exudate disappeared and papillœdema slowly regressed, though in only 1 case out of 6 did it entirely disappear

Exercise Tolerance during Treatment

When exercise tolerance had been seriously reduced by hypertensive disease, it improved greatly when the blood-pressure was lowered A patient who, when first seen, could walk only a few yards without gross dyspnœa was able, after seven months' treatment with pentacynium alone, to walk 500 yards without undue effort In hypertensive patients the blood-pressure often rises sharply during exercise, pentacynium prevented this In several patients under treatment the diastolic pressure fell during exercise, particularly when this involved mainly the leg muscles

Value of the Test Dose

A patient who had a good response to a parenteral test dose did not always do well on long-term oral treatment, but a patient who responded poorly to an adequate test dose invariably did badly

Combination with Reserpine and other Drugs

As with hexamethonium, pentolinium, chlorisondamine, and mecamylamine, introduction of the alkaloids of rauwolfia into the treatment produced an additional fall in blood-pressure On average (13 patients), reserpine 0 25 mg t d s further lowered the systolic and diastolic blood-pressure, both in the supine and standing positions, by approximately 10–20 mm Hg Unlike that caused by the ganglion-blocking agents, this additional fall did not depend mainly on posture, and affected the systolic and diastolic pressures to a similar extent In this respect our findings agree with those of Cooper and Cranston (1957) The close agreement between the degree of lowering of blood-pressure by reserpine alone obtained by these workers and the additional lowering in blood-pressure obtained in our series by adding reserpine to ganglion-blocking therapy strongly suggests that the effects of these drugs are additive and not synergistic

Cessation of pentacynium therapy while reserpine was continued caused the systolic and diastolic pressures to revert to within 20 mm Hg of their control levels

The introduction of reserpine into therapy enabled the dose of pentacynium to be reduced in some cases The incidence of side-effects was thereby lowered and more effective control of the blood-pressure achieved Reserpine caused no depression

Effect of Anion on Activity

Harington and Rosenheim (1954) reported that the oral absorption of hexamethonium depended to some extent on the anion In this investigation three salts of pentacynium were tested—namely, the chloride, the sulphate, and the bis-methylsulphate Provided the dosage was adjusted to take account of the differences in molecular weight, there was no detectable difference in therapeutic activity All three salts are almost completely ionised in aqueous solution at the concentrations used, and this would be expected to lead to independent absorption of the anion and cation both from the injection-site and from the gut

In this study prolonged administration of pentacynium produced no significant change in the blood picture, and there was no local or generalised toxic reaction after its parenteral or oral use

Side-effects

As with pentolinium, chlorisondamine, and mecamylamine, the side-effects of pentacynium are due mainly to associated parasympathetic blockade, and nearly all the patients experienced some discomfort during the early stages of treatment The incidence of the main side-effects is shown in table III

After some weeks of treatment, the side-effects tended to become less severe, and in only 3 cases were the long-term side-effects severe enough to require cessation of treatment In a further 9 patients side-effects, mainly

TABLE III—NATURE, NUMBER, AND SEVERITY OF SIDE-EFFECTS IN 30 PATIENTS

—	Early		Late	
	Severe	Mild	Severe	Mild
Side-effects				
Blurring of vision	10	13	1	6
Dry mouth	—	11	—	1
Constipation	—	5	—	2
Postural hypotension	2	5	—	2
Nausea and vomiting	1	4	—	2
Impotence	1	—	1	—
Muscular weakness	—	2	—	—
No symptoms	3		18	
Inconvenience	24		9	
Disabling symptoms	3		3	

blurring of vision and postural faintness, persisted and gave rise to some discomfort, though they were not severe enough for the patient to demand the stopping of treatment

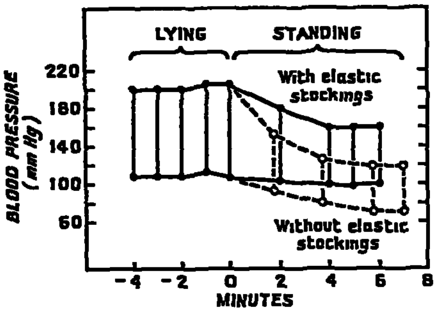

Fig 5—Effect of elastic stockings on blood-pressure fall in standing position

Control of side-effects—Blurring of vision was controlled by one drop of 0 1% pilocarpine instilled into the conjunctival sac once or twice daily Constipation, when it occurred, was treated with laxatives 1 patient, who occasionally had severe symptoms of postural hypotension but whose dose it was considered unwise to reduce, was greatly helped by wearing elastic stockings, which reduced the postural fall in blood-pressure (fig 5)

Comparison and Scheme of Treatment

Comparison with other ganglion-blocking substances was possible in 10 patients—with pentolinium in 5 and with mecamylamine in 5

3 patients in whom pentolinium had previously been discontinued because of side-effects were satisfactorily controlled on pentacynium, the other 2 showed little change in control of blood-pressure or in side-effects Of the 5 patients who also received mecamylamine, 3 were classed as non-responders to both this and pentacynium, 1 was equally well controlled with either drug, and 1 had a smaller blood-pressure fall and fewer side-effects with mecamylamine

Although each patient in this study received an initial test dose of pentacynium by subcutaneous injection, there appears to be no reason why treatment should not start with a small oral dose of 50 mg two or three times daily, provided the blood-pressure can be recorded frequently, this dose may then be increased by 25 mg every two days until stabilisation is achieved If reserpine is to be used in addition, it should be started about a week before the ganglion-blocking therapy

Discussion

Our preliminary experience with pentacynium suggests that it is an effective and useful agent in the treatment of severe hypertension The dissociation between the sympathetic and parasympathetic blocking actions has redistributed rather than reduced the incidence of side-effects Severe constipation has in our experience not been as common as with other similar drugs

The dose of reserpine (0 25 mg t d s) used to enhance the hypotensive effect in this study is rather higher than that at present generally recommended (0 1 mg t d s)

With regard to the selection of patients for treatment, we consider that in the present state of knowledge the use of ganglion-blocking agents is unjustifiable in symptomless essential hypertension, and that only in exceptional cases should they be used when the blood non-protein-nitrogen is 50 mg or more per 100 ml

Finally, in our experience pentacynium, like other ganglion-blocking agents, requires a considerable effort on the part of the doctor to guide the patient through the initial period of treatment, when side-effects may be troublesome Success in the treatment of hypertension with ganglion-blocking agents depends more on the doctor's management of the patient than on the use of any individual drug

Summary

Pentacynium bis-methylsulphate ('Presidal') was administered by injection and orally to 30 hypertensive patients for periods of up to eighteen months

The blood-pressure was adequately controlled in 24 of these 30 cases Reserpine 0 25 mg t d s increased the hypotensive effect by 10–20 mm Hg

The side-effects were similar to those of other ganglion-blocking substances, but constipation was less severe

We thank Dr E Noble Chamberlain and Dr Robert Coope for their interest, advice, and help, and the consultant physicians, registrars, house-physicians, sisters and nurses of the Sefton General Hospital, Liverpool, for their ready cooperation The material used in this investigation was supplied by Burroughs Wellcome & Co

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METHYLPENTYNOL CARBAMATE

PHARMACOLOGICAL AND CLINICAL INVESTIGATIONS

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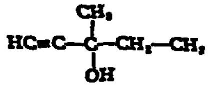
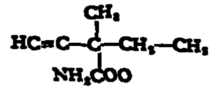
In the search for a drug as innocuous as methylpentynol (Trotter 1953, Bourne 1954, Gusterson 1955) methylpentynol carbamate was produced

Methylpentynol



$$HC{\equiv}C{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}{-}CH_2{-}CH_3$$

Methylpentynol carbamate



$$HC{\equiv}C{-}\overset{\displaystyle CH_3}{\underset{\displaystyle NH_2COO}{C}}{-}CH_2{-}CH_3$$

Investigations by the manufacturers showed that methylpentynol carbamate has an oral LD_{50} in mice of 337 mg per kg (limits 320–348 mg) An intravenous dose of 0 01 g had no effect on blood-pressure or respiration in the cat or rabbit, and doses of 50 mg per kg had no analgesic properties in mice when tested by the hot-stage method

No gross lesions were found at necropsy in mice which had had the drug by mouth for five months at two dose levels (170 and 85 mg per kg daily)

Results of metabolic experiments by us using the method of Perlman and Johnson (1952) were inconclusive, but they did indicate that methylpentynol carbamate may be rapidly metabolised by the liver, kidney, and brain tissue in vitro, and the liver and kidney seemed to be more effective than the brain

Investigations on Volunteers

Respiratory System

6 volunteers recorded their respiratory-rates and minute-volumes by breathing into a gas-meter B M C apparatus (McKerrow 1953), using a Parkinson and Cowan gas-meter calibrated in litres Readings were obtained at four-minute intervals for twelve minutes before administering 200 mg of methylpentynol carbamate in a single dose, and subsequently at frequent intervals for ninety minutes 4 patients, who had received doses of 100 mg per stone body-weight as premedication, were similarly tested No significant alteration in respiratory-rate or minute-volume was demonstrated in any of the 10 subjects

Cardiovascular and Hæmopoietic Systems

(*a*) 3 subjects who had doses of 100 mg per stone body-weight as premedication had electrocardiograms recorded before taking the drug and at intervals of thirty and sixty minutes afterwards No significant changes were seen

(*b*) 6 healthy volunteers received 200 mg of methylpentynol carbamate Their blood-pressures were taken at five-minute intervals for twenty minutes before administration and every ten minutes for sixty minutes afterwards There was no significant alteration in either the systolic or the diastolic pressure 26 adults received 100 mg per stone body-weight of methylpentynol carbamate before anæsthesia Those whose blood-pressures were within the normal range showed no change In hypertensive patients the systolic fall (20–50 mm Hg) which usually follows premedication was observed

(*c*) 4 healthy volunteers were given 100 mg night and morning for ten days to see whether there was any cumulative toxic effect Red, differential white, and platelet counts were taken the day before medication, on the fourth day, and the day after it was stopped The counts were unchanged

Liver Function

The same volunteers were seen before breakfast on four occasions—the day before medication, the fourth and eighth days of medication, and the day after medication was stopped 15 ml of blood was withdrawn at each visit by a self-retaining venous cannula, which was then sealed and left in situ Sulphobromophthalein (5 mg per g body-weight) was injected into a vein in the opposite arm, and at twenty and forty minutes later, 10 ml of blood was withdrawn through the cannula for plasma-dye estimations 10 ml of the original specimen was used as a control for the sulphobromophthalein test, the remainder being used for the van den Bergh and serum-alkaline-phosphatase tests The results of these tests suggested that the liver was unaffected by the medication

Kidney Function

Daily specimens of urine from the 4 volunteers were analysed and examined microscopically No abnormality was found

Electroencephalogram

Electroencephalograms were recorded in 5 volunteers before and sixty minutes after a preoperative dose of 100 mg per stone body-weight The readings were compared with those in 2 patients who had pentobarbitone (gr $^{1}/_{2}$ per stone body-weight) After barbiturates there was an increase in fast activity similar to that associated with deep sleep With methylpentynol carbamate there was little increase in fast activity unless the patient did fall asleep

Reaction-time and Muscular Coordination

Tests were carried out, using methylpentynol carbamate, similar to those described for methylpentynol (Trotter 1954) Results were of the same order As with methylpentynol reaction-times after methylpentynol carbamate were *decreased* (not increased as after alcohol or pentobarbitone) Muscular co-ordination tests were normal (Apparatus used McDougal-Schuster dotter apparatus and motorcar cockpit supplied by the Royal Society for the Prevention of Accidents) (Moreover, the drug has been administered by us to over 10,000 ambulant patients, with no apparent impairment of reaction-time)

These preliminary investigations disclosed no side-effects, but we ourselves took increasing doses to try to establish a safe maximum Single doses of 1200 mg produced no drowsiness, ataxia, or digestive upset, though there was sometimes a slight "hot feeling" in the gullet

Clinical Studies

Patients tolerated 100 mg of methylpentynol carbamate per stone body-weight, and this dose produced similar preoperative sedation to pentobarbitone (gr $^{1}/_{2}$ per stone body-weight), but with certain qualitative differences described later

Premedication for Dental Operations under Local Anæsthesia

Methylpentynol carbamate was given to over 10,000 ambulant outpatients in the following dosage

Patients without visible sign of apprehension	2 × 100 mg tablets
Mildly apprehensive patients	4 × 100 mg tablets
Very apprehensive patients	100 mg per stone body-weight

Children were given up to four tablets routinely, but those who were very apprehensive or uncontrollable were given higher doses, proportional to body-weight, without untoward effect

Of the 10,000 patients thus treated, 90% showed no apprehension during operation, 7% were apprehensive, and 3% were very apprehensive In some of the patients in the last two groups (7% and 3%) the dose was augmented to 100 mg per stone body-weight (if a smaller dose had previously been given) immediately their apprehension was apparent after the start of the operation After a suitable pause the operation began again, and their apprehension was then removed or much reduced Hilarity and loquacity, occasionally noticed with methylpentynol (Trotter 1954), were negligible

Methylpentynol carbamate took longer to act than methylpentynol, but the effect lasted longer This is an advantage when operations are long or when postoperative sedation is needed The delayed onset may be a disadvantage when the drug is given to a patient at the surgery, but, if taken before the patient left home, methylpentynol carbamate could conceivably relieve the "waiting-room" apprehension and still be effective during the operation

Premedication in Ambulant Patients before Dental Extractions under General Anæsthesia

The 373 patients in this group consisted of those who showed much apprehension on arrival, those who were accustomed to premedication, those who, after settling in the dental chair, resolutely refused the anæsthetic, and children with a history of toothache who had been so upset that intra-oral examination on admission was impossible

31 received elixir of methylpentynol orally (250–750 mg), 40 received methylpentynol carbamate orally (200–1000 mg), 82 received methylpentynol carbamate orally and hyoscine (gr $^{1}/_{300}$–$^{1}/_{150}$) sublingually, and 63 received hyoscine alone

Further comparisons were afforded by 101 patients who received pentobarbitone orally (gr $^{1}/_{2}$–$2^{1}/_{2}$), 13 who had pentobarbitone orally and hyoscine (gr $^{1}/_{300}$–$^{1}/_{150}$) sublingually, 14 who had pethidine intravenously (20–34 mg), 26 who had chloral hydrate orally (gr 5–8), 2 who had phenobarbitone sodium orally (gr 1), and 1 who had promethazine-8-chlorotheophyllinate ('Avomine') 50 mg orally and hyoscine gr $^{1}/_{150}$ sublingually

Pentobarbitone (gr $^{1}/_{2}$ per stone body-weight), used for years, has been discarded by some anæsthetists because it caused a great deal of ataxia and sleepiness during recovery A dose of gr $^{1}/_{4}$ per stone combined with sublingual hyoscine (gr $^{1}/_{150}$–$^{1}/_{75}$) solved this problem, but failed to provide adequate sedation On this dosage the average time between recovery and going home was over forty-four minutes (13 cases), whereas with methylpentynol carbamate and hyoscine this was reduced to under twenty-seven minutes (82 cases)

Methylpentynol had the disadvantage, with general anæsthesia, that it had to be taken with water (or fruit-juice) only a quarter or *half an hour* before induction, and occasionally there was vomiting Methylpentynol carbamate eliminates this disadvantage, for it can be given *an hour or more* beforehand

REACTION TO INTRAVENOUS INJECTION IN CHILDREN (INDUCTION OF ANÆSTHESIA)

Premedicants	No *of* cases	*Flinch*	With-drawal	*Struggle*	Gas given before intra-venous injec-tion
Pentobarbitone and atropine	89	33 (*37%*)	29 (*33%*)	27 (*30%*)	33 (*37%*)
Pentobarbitone and hyoscine	26	10 (*38%*)	8 (*31%*)	8 (*31%*)	10 (*38%*)
Methylpentynol carbamate and atropine	21	8 (*38%*)	1 (*5%*)	0	2 (*10%*)
Methylpentynol carbamate and hyoscine	36	12 (*33%*)	0	0	3 (*8%*)
Papaveretum and hyoscine	28	4 (*14%*)	0	0	1 (*4%*)

As hyoscine reinforces the action of pentobarbitone, it was used with methylpentynol carbamate It was given sublingually in tablet form in doses of gr $^1/_{150}$ to children up to the age of 12 years and gr $^1/_{75}$ to those above this age With this regimen, sedation was seen at its best Patients who had been agitated, apprehensive, or completely unmanageable sat down quietly and, for the most part, accepted induction with complete equanimity Nearly 80% of these had refused to have gas only sixty to ninety minutes previously

Only 5 patients who had methylpentynol carbamate were sleepy on recovering from the anæsthetic

Premedication before General Surgical Operations under General Anæsthesia

Methylpentynol carbamate, with either hyoscine or atropine, was given to 96 children (age 2 to 14 years) for tonsillectomy and adenoidectomy or both, and the results were compared with those after pentobarbitone premedication, which has been given previously for these operations In addition, 26 adults were premedicated with methylpentynol carbamate and hyoscine before various operations In all these cases the methylpentynol carbamate was given by mouth and the hyoscine by subcutaneous injection

In 42 tonsillectomies, methylpentynol carbamate was given at varying times before operation, the effect was greatest between one and two hours after administration Preoperative cooperation was good in 33, poor in 8, and bad in 1 9 arrived at the anæsthetic room asleep Of the 8 in whom cooperation was poor, 5 had received their methylpentynol carbamate four hours previously, 2 three hours previously, and 1 two hours previously Subcutaneous atropine (gr $^1/_{100}$) was administered three-quarters of an hour before operation

In 54 tonsillectomies, atropine was replaced by hyoscine (gr $^1/_{200}$) subcutaneously Cooperation was good in 49, poor in 4, and bad in 1 Of the 4 with a "poor" response, 3 had received methylpentynol carbamate four hours previously, and 1 one hour previously

In these two series only 28% of the children and 15% of the adults were restless during recovery from anæsthesia In a control series, using pentobarbitone premedication, 93% of 148 patients were restless

When methylpentynol carbamate is used, the recovery is hastened compared with that from pentobarbitone, and the protective throat-reflexes are soon in operation The likelihood of blood being inhaled after tonsillectomy or other operations within the mouth is minimised, and less nursing-time is taken up in looking after semiconscious children

Papaveretum and hyoscine gave the best results, and most adverse reactions were seen when pentobarbitone was used, though hyoscine, when added, gave slightly better results than atropine Pentobarbitone cannot be relied on to make children accept intravenous anæsthesia, and for those who are still averse to giving papaveretum to children methylpentynol carbamate offers an attractive alternative At the preoperative follow-up injection of atropine or hyoscine after methylpentynol carbamate, slight flinching was the rule, there was no withdrawal or struggling This lack of response to needle-prick has an added advantage in that only one nurse is needed to give the preoperative follow-up injection of atropine or hyoscine, which is not true of barbiturate premedication

Discussion

As a general rule the barbiturates seem to act in two ways they depress certain inhibitory mechanisms, so increasing the reflex irritability of the greater part of the central nervous system, and they depress the reticulo-activating centre, so causing loss of consciousness With barbiturates, an increased nervous irritability is shown by an exaggerated response to painful stimuli, a tendency to laryngospasm, and restlessness during recovery Some barbiturates are central convulsants, with no hypnotic properties whatever (Cope and Hancock 1939, Knoefel 1945)

After barbiturates, withdrawal or struggling is the usual reaction to an intravenous needle, but after papaveretum or methylpentynol carbamate the patient rarely reacted adversely (see table) Either methylpentynol carbamate is to some extent analgesic, or it provides a central nervous sedation in contrast to the increased nervous excitability produced by the barbiturates The fact that hypnosis is rare with methylpentynol carbamate deceives those accustomed to using barbiturates into assuming that the sedative powers of methylpentynol are less than they really are, but the use of methylpentynol carbamate 800 mg three-hourly in childbirth has led to the suggestion that in high dosage it may be analgesic (Barnett, personal communication)

We have not seen laryngeal spasm after giving methylpentynol carbamate, except in the pilot investigation when some patients were given the drug as long as two and a half to four hours before anæsthesia This is in sharp contrast to those given barbiturates Methylpentynol carbamate, therefore, provides a much easier changeover to ether after induction with nitrous oxide and oxygen, and laryngospasm is rare during those throat operations when light anæsthesia is maintained and an endotracheal tube is not used The drug does not cause respiratory depression, so it is safer to use intravenous anæsthesia after methylpentynol carbamate than after barbiturates

Conclusions

Results of tests with methylpentynol carbamate, and observation of over 10,000 patients to whom the drug was given, suggest that it has low toxicity and no undesirable side-effects

The delayed onset and longer action of methylpentynol carbamate have many advantages, but they become disadvantageous when a rapidly acting short-duration drug is needed Methylpentynol itself is then the drug of choice

We should like to thank Prof C H Gray, Dr E D Lawrence, Dr W M Davidson, and Dr S Nevin for their help Our thanks are also due to Miss M Hall, Dr Margaret Rooms, Dr William T Henry, Dr N Tate, Miss O Jenkins, Mr G H Wilkinson, the students of King's College Hospital who took part in the tests, and the sisters and nurses at various hospitals for their cooperation British Schering, Ltd, supplied the methylpentynol carbamate ('Oblivon-C')

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METHYLPENTYNOL CARBAMATE AND LIVER FUNCTION

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Methylpentynol carbamate (methyl 1–3-pentyne-1-ol-3 carbamate) is a recently introduced derivative of methylpentynol ('Oblivon'), its pharmacology having been studied by Halpern (1956) and Halpern and Lehmann (1956) and a clinical appraisal coming from Kourilsky and Kourilsky (1957)

Schaffarzick and Brown (1952) had produced evidence that methylpentynol was potentially hepatotoxic, but Kennedy and Trounce (1955) averred that it had no untoward effect on liver function Nevertheless, since the carbamate is stated to be three or four times as potent as the parent substance, we considered it worth while to exclude any possibility of an adverse action on the liver

Methods

12 patients (7 male and 5 female), aged 28–49, weighing 33 6–88 2 kg, and having various diseases, were therapeutically prescribed methylpentynol carbamate 1–3 g daily for two to seven weeks, no other drugs being concurrently administered Patients likely to be exceptionally susceptible to drugs—e g, those with anæmia, and those with either a history or evidence of hepatic and renal damage—were excluded

All the patients were seen daily throughout the investigation A battery of liver-function tests relating to excretory function and to protein metabolism were applied initially during a seven-day control period when the patient was receiving inert tablets, and thereafter weekly while methylpentynol carbamate was being prescribed, a further series of control values being obtained two weeks after the end of therapy

The methods and values for the liver-function and other tests were as follows bile pigments, Fouchet's test, bile salts, Hay's test, urinary urobilin, Schlesinger's fluorescence method, and urinary urobilinogen, Ehrlich's aldehyde test on an early morning specimen of urine, the results for both being graded from 0 to 4+ with a 1+ or greater regarded as abnormal, serum-bilirubin, serum treated with diazo solution followed by alcohol and saturated ammonium sulphate, a normal value being less than 1 mg per 100 ml, alkaline phosphatase, method of King and Armstrong, with a normal range of 3–13 units, total plasma-proteins, normal range 5 8–8 6 g per 100 ml, serum-albumin, 3 4–6 7 g per 100 ml, serum-globulin, 1 2–2 9 g per 100 ml, preliminary separation being achieved with 26% sodium sulphate and estimation by the micro Kjeldahl method (Harrison 1949), thymol turbidity, method of Maclagan (1944), the normal range being 0–4 units, the grading of 0–4+ of Maizels (1946) also being adopted, with ± representing fine granularity without precipitation, usually over the range of 4–8 units, thymol flocculation, method of Neefe (1946), the result being graded only as negative or positive, zinc-sulphate reaction (normal, 2–8 units) by the turbidimetric technique of Kunkel (1947), cephalin-cholesterol test, with flocculation graded from 0–4+ and read at twenty-four and forty-eight hours, readings of 2+ or greater being deemed abnormal, prothrombin time (Quick's test) with thromboplastin supplied by Difco and done concurrently on the patient and a control, erythrocyte-sedimentation rate (E S R) (Westergren), the values adopted being those suggested by Westergren (1957) of an upper limit of normality of 5 mm at one hour for males and 12 mm at one hour for females

The remaining investigations such as the blood film, white-cell count and differential, hæmoglobin, and routine testing are too familiar to require amplification

Results

No abnormalities were discovered in the tests for bile salts or pigments, urinary urobilin, serum-bilirubin, alkaline phosphatase, total plasma-proteins, serum-albumin and serum-globulin, zinc-sulphate or cephalin-cholesterol reactions, prothrombin-time, hæmoglobin values, blood film, and white-cell count and differential

The positive abnormalities found were as follows

Tests of Excretory Function

Urobilinogen (grading 1+) was detected in the urine of cases 8 and 11 during the final two and three weeks of the drug regime, reverting to normality two weeks after withdrawal of the carbamate At no time was either patient pyrexial

Tests of Protein Metabolism

A *thymol-turbidity* reading of 5 units (control value 3 units) with a ± grading was noted in cases 8 and 9 during the last week of treatment with methylpentynol carbamate The *thymol-flocculation test* also became positive in case 12 during the final week of treatment with methylpentynol carbamate

Other Tests

A presumed significant increase of the E S R in the absence of either intercurrent illness or pyrexia was noted for 2 males in case 9 the reading increased from a control value of 5 mm at one hour to 15 mm and 17 mm at one hour during the last two weeks of treatment with methylpentynol carbamate, in case 12 the E S R rose from the control value of 4 mm at one hour to 14, 12, and 17 mm at one hour in the last three weeks of treatment with methylpentynol carbamate

Urine a substance reducing Benedict's solution (blue to orange) was noted in the urine of case 12 during the last three weeks of treatment with methylpentynol carbamate

Other Drug Effects

An unexpected high incidence of toxic effects referable to the central nervous system was also evident, the time sequence of which, together with the scheme of dosage for the drug, is depicted in fig 1 These complications occurred in 11 cases but only when the dose of methylpentynol carbamate exceeded 1 g by mouth daily The individual signs and symptoms are displayed in fig 2

The mildest toxic phenomena amounted to behavioural changes—e g, drowsiness, slight disturbance of mood—and

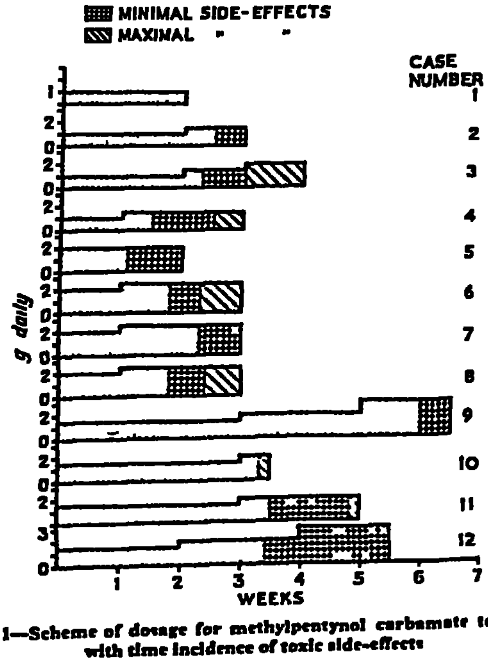

Fig 1—Scheme of dosage for methylpentynol carbamate together with time incidence of toxic side-effects

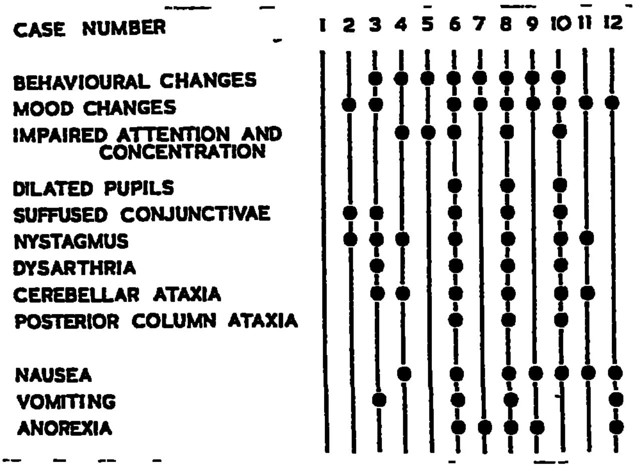

Fig 2—Individual incidence of abnormal symptoms and signs with methylpentynol carbamate.

physical signs, including suffusion of the conjunctivæ, with nystagmoid jerks of the eyes on conjugate lateral gaze. These minimal abnormalities presented without further development and without meriting withdrawal of methylpentynol carbamate in 5 patients (cases 2, 5, 7, 9, and 12), and being the precursor to a much more dramatic picture in 5 others (cases 3, 4, 6, 8, and 11). These last-named patients displayed intense affective disturbance (symptomatic depression and irritability) combined with signs such as pupillary reflex anomalies, sustained nystagmus on conjugate lateral deviation of the eyes, diplopia, ptosis, loss of tone in the lower facial musculature, dysarthria, and tremor of the outstretched tongue. Cerebellar and posterior-column deficits and ataxy were noted in the limbs.

When it was found that these maximal toxic reactions did not abate if methylpentynol carbamate was still administered (cases 3, 4, 6, and 8), the appearance thereafter of such features was the signal for instant withdrawal of methylpentynol carbamate. It can therefore probably be inferred that, at the higher dosage levels, methylpentynol carbamate accumulates in the body.

Severe anorexia and nausea developed during treatment with methylpentynol carbamate in 7 patients (cases 4, 6, and 8–12), and even vomiting unrelated to food and presumably ascribable to methylpentynol in cases 3, 6, 8, and 12.

Full recovery invariably ensued within five days of the withdrawal of methylpentynol carbamate.

Discussion

The mild disturbance found in tests for hepatic excretory and metabolic function seems to indicate that methylpentynol carbamate can exert a toxic action on the liver. No more precise statement is feasible, because the methylpentynol was not prescribed for longer than seven weeks, and because of the extremely high dosage administered. Any indictment is therefore slender; in fact none of the test abnormalities appeared unless the patient was receiving at least 2 g of methylpentynol carbamate daily. It therefore seems fair to remark that, if the dosage of methylpentynol carbamate does not exceed 1 g daily, the liver-function tests are not likely to be found abnormal.

Other untoward effects of methylpentynol in large dosage were reflected in the alterations of the mental state, particularly deviations of mood, and in physical signs indicating involvement of central nervous system function, especially the cranial nerves and the cerebellar and posterior-column connections to the limbs. Similar phenomena have been observed in methylpentynol intoxications (Marley and Chambers 1956) and after ethanol (Howells 1952, 1956). No clinical side-effects have been noted with either single oral doses of 0·1–1·0 g of methylpentynol carbamate (A. H. Galley, personal communication) or after 0·8 g three-hourly during labour (V. H. Barnett, personal communication).

The reducing substance found in the urine of 1 patient towards the end of methylpentynol therapy was presumably a conjugate of methylpentynol with glycuronic acid, because Perlman et al. (1953) demonstrated that a breakdown product of methylpentynol was excreted in the urine as a glycuronate.

Summary

Methylpentynol carbamate was administered to 12 patients in dosages of 1–3 g by mouth daily for from two to seven weeks.

Mild disturbances of hepatic excretory function (urinary urobilinogen) and protein metabolism (thymol turbidity and flocculation) were observed. Increase in the E.S.R. was also noted, and a reducing substance was found in the urine. There was no alteration in the blood picture.

Side-effects attributable to methylpentynol included anorexia, nausea and vomiting, alterations in the mental state, and the appearance of such signs as nystagmus, pupillary anomalies, ptosis, loss of tone of the lower facial musculature, dysarthria, and cerebellar and posterior-column ataxia.

None of these abnormalities seem likely to develop on a daily oral dose of 1·0 g or less of methylpentynol carbamate.

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ACUTE STREPTOCOCCAL MYOSITIS

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SPONTANEOUS acute streptococcal myositis, which is occasionally found in the tropics (Manson-Bahr 1954), has seldom been reported in England, so four fatal cases seen in the postmortem room of Addenbrooke's Hospital in 1951–56 may be of interest.

Case-reports

FIRST CASE

A farmer's wife, aged 33, returned from a holiday in Scotland on Oct. 8, 1951, with a cold which caused her to lose her voice for a day or two; within a week, however, her cold had gone, and on Oct. 15 she seemed quite well. Next morning (Oct. 16) she ached all over and felt cold and shivery; after lunch she vomited twice and began to complain of pain in the left leg

This pain increased in severity and by the evening the limb was swollen

Next day (Oct 17) the pain was rather less severe, but she still felt unwell, and in the afternoon she was visited by her doctor, who found that her temperature was 103°F Arrangements were made for her to be admitted to hospital next day, but in the evening her relations noticed that she was becoming difficult to talk to and did not seem to know what was going on The doctor was called again and sent her to Addenbrooke's Hospital as an emergency She was admitted at 12 30 A M on Oct 18 restless, dyspnœic, cold, and sweating, with radial pulses barely perceptible and very rapid (rate about 140 a minute), blood-pressure 70/40 mm Hg, and temperature 102 6°F Her left thigh was œdematous and hot, the skin over it being cyanotic, with a patchy lividity Her urine contained albumin and acetone She was given penicillin and aureomycin intravenously, but within half an hour of admission she was unconscious and apparently moribund, and at 1 55 A M she died

Previous History

Since the age of 17 she had had occasional "running sores", rather like small boils, which came out occasionally on all parts of her body For these she received a course of penicillin injections three years before her final illness After this she had only a few of these sores, and none recently For about ten years she had also at times had painful lumps which appeared near joints, especially on her hands and feet, and lasted a day or two She also had "a form of rheumatism", with some stiffness of the limbs and joints

Necropsy Findings

Acute suppurative streptococcal myositis of the left quadriceps femoris muscle, which was pale and abnormally soft, with the individual fasciculi of muscle-fibres separated by thin greenish-yellow pus The purulent infiltration extended up to the groin and down to the knee Moderate œdema but no purulent infiltration of the left leg below the knee Moderate excess of turbid glairy brownish-pink fluid, probably containing inflammatory exudate, in the left knee-joint, with conspicuous hyperæmia of the synovia of the joint but no erosion of the articular cartilage Slight excess of almost clear glairy brownish-pink fluid in the otherwise normal left hip-joint Left femur, tibia, and fibula normal externally and on bisection, with no evidence of osteomyelitis No abnormality of adductor or hamstring muscles of left thigh

Hyperæmia of skin of inner aspect of left thigh above the middle, with several recent bullæ on the hyperæmic area These bullæ were not observed during life and must be regarded as agonal Several small pitted scars around both knees, and one on the back of the left thigh No recent septic lesions on skin of thigh or elsewhere, except the bullæ already mentioned No thrombosis of veins of left lower limb, although the femoral and popliteal vessels passed through purulent tissues

Considerable inflammatory enlargement of left inguinal and iliac lymph-nodes No hæmolytic staining of the lining of aorta or other blood-vessels Swollen ill-defined malpighian bodies in bright purple-red pulp of slightly enlarged spleen Blurred pattern in swollen suprarenal glands A few purple-red radial streaks, but no abscesses, in cortex of kidneys No pneumonia or abscesses in greatly congested lungs Tonsils absent Some cloudy swelling of myocardium, heart valves normal Cyanosis of fingers A well-nourished woman

Microscopical and Bacteriological Examination

The purulent exudate in the left thigh contained very numerous streptococci, the left inguinal lymph-nodes were acutely inflamed, and severe parenchymatous degeneration was seen in the kidneys, excessive leucopoiesis in the bone-marrow, and slight centrilobular large-droplet fatty change in the liver

Cultures from the affected muscles grew hæmolytic streptococci of group A, type 4, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol Two cultures from the spleen were examined, one was sterile, but the other yielded a few colonies of streptococci

SECOND CASE

A man, aged 33, by occupation a market trader, was admitted to Addenbrooke's Hospital on Oct 27, 1952, complaining of severe pain in his left thigh He said that the pain had begun the day before, it then prevented him from walking, and he had stayed in bed all day, sweating much

On admission he was distressed and sweating, with temperature 103 2°F, pulse-rate 132, respirations 20 a minute There was swelling and acute tenderness of the lower anterior part of the thigh, down to and including the patellar region, with erythema of the skin Examination of his blood showed hæmoglobin 16 2 g per 100 ml, leucocytes 23,000 per c mm (neutrophils 84% = 19,320 per c mm, juvenile forms 6% = 1380 per c mm, neutrophil myelocytes 0 5% = 115 per c mm)

Treatment and Course

The patient had been given an injection of penicillin before admission, and at 8 P M another was given (500,000 units) A blood-culture taken at 11 30 P M proved to be sterile Further injections of penicillin 500,000 units were given three-hourly until his death on Oct 29 (total dosage 6,000,000 units) On Oct 28 he appeared very toxic and ill, his temperature was down to 98 4° F, but his pulse-rate remained 130

Operation—Under general anæsthesia an incision was made into the lateral aspect of his left thigh Pus was observed coming from the under-surface of the rectus femoris muscle, and much of this muscle and the vastus lateralis muscle appeared necrotic it did not bleed or contract No pus was found around the femur, which looked healthy Necrotic muscle was removed until healthy tissue appeared Thin watery purulent fluid oozed from the cut surface of the necrotic muscle, but no gas was seen, nor were there any localised abscesses The incision was closed with nylon sutures placed wide apart The patient was now given aureomycin 250 mg four-hourly, and later terramycin in an intravenous drip, but his condition steadily deteriorated, his pulse-rate rose to 200, and he died at 10 30 A M on Oct 29, apparently of extreme toxæmia

Necropsy Findings

Acute suppurative streptococcal myositis of left thigh Thin pinkish-red purulent fluid exuded from the partially necrotic remnants of the left vastus lateralis and rectus femoris muscles Similar exudate in fascial planes of the thigh from popliteal fossa almost to the groin Surgical incision on lateral aspect of the left thigh Adductor and hamstring muscles of left thigh almost normal in appearance Left femur and hip- and knee-joints normal Acute inflammatory swelling of left inguinal lymph-nodes Slight general enlargement of lymph-nodes Very soft purple-grey acute septic spleen Pale red-brown myocardium and normal heart valves Congestion and œdema of heavy dark purple-red lungs *Pale yellow patches* on surface of swollen yellow-brown liver The capsules stripped easily from the surfaces of the pale kidneys No pyæmic abscesses found in any organ A well-nourished young man

Microscopical and Bacteriological Examination

Acute purulent myositis of the left thigh Gram-positive cocci were abundant in some parts of the section, but many appeared degenerate and had lost their gram-positive staining, many had been phagocytosed by leucocytes Severe acute inflammatory changes were present in the spleen, but no bacteria were seen in a gram-stained preparation Numerous leucocytes were crowded in the sinusoids in some parts of the liver *Parenchymatous* degeneration of kidneys Congestion, hæmorrhages, and œdema of lungs

Cultures of the purulent fluid from the left thigh muscles (operation specimen) gave a profuse growth of hæmolytic streptococci of group A, type 3, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol Nose and throat swabs were taken on Oct 31 from each of the four members of the patient's household No hæmolytic streptococci were isolated from any of these swabs

THIRD CASE

A housewife, aged 76, was admitted to Addenbrooke's Hospital on May 24, 1953 She was too ill and confused to give a history, but according to her relatives her illness had begun five days previously, when she had complained of pain in her face, for this she had applied a liniment. Next day she had pain in her left thigh and aching in all joints, a red patch "as big as a tennis ball" appeared on the outer aspect of her left thigh Her nose was now swollen, and a scab formed on it Two days later (two days before admission) she seemed very ill, her breathing was "very heavy" and her lips and cheeks looked blue, but she was said not to have been febrile Malaise and general weakness continued, and the day before admission she fell down while walking to the lavatory

On examination she was extremely ill, with signs of peripheral circulatory failure Her nose, ears, and extremities were deeply cyanosed and her features pallid Her temperature was 100°F and systolic blood-pressure 55 mm Hg, the diastolic pressure could not be recorded, the pulse was of poor volume (rate 140) A scabbed lesion about 2 cm in diameter was present on her nose Her left leg was swollen, especially the thigh, which was very tender on its lateral aspect All movements of this limb were very painful, it was held externally rotated In view of the history of a fall, the possibility of a fracture of the neck of the left femur was considered, but the first need obviously was for treatment of the profound circulatory failure, which was thought possibly to be due to septicæmia, to pulmonary embolism, or to myocardial infarction Treatment with intravenous infusions, 'Eucortone', penicillin (500,000 units), and nikethamide was, however, of no avail, and the patient died in coma about seven hours after admission

Previous History

Rickets in childhood, and winter cough and "rheumatism" for years

Necropsy Findings

Acute streptococcal myositis of the left thigh Thin yellow-pink fluid exuded from the pale grey-pink cut surfaces of the vastus lateralis and adjacent muscles of the left thigh, there was one moderately well-defined abscess (1 5 cm in diameter) containing thick creamy-yellow pus deep in the substance of the vastus lateralis muscle, with several smaller abscesses near it No thrombosis or other abnormality of the veins of the left lower limb Left femur, knee-joint, and hip-joint normal Several superficial bullæ (largest 4 × 2 cm) containing clear reddish fluid on skin of posterolateral aspects of left thigh just above the knee No septic lesions of any kind on the rest of the skin of the left leg, the search particularly included the clefts between the toes Rather soft and pale normal-sized spleen (125 g) No hæmolytic staining of aorta or other blood-vessels Moderately severe atheroma of coronary arteries, with narrowing and calcification Rather flabby brownish-red myocardium Heart valves functionally normal and devoid of vegetations Congestion and bullous emphysema of rather small lungs Patchy centrilobular congestion in pale liver Blurred pattern on cut surfaces of suprarenal glands (acute inflammatory swelling) One dry crusted lesion (2 cm in diameter) on the left side of the nose Mild osteoarthritic changes and Heberden's nodes in both hands A moderately well-nourished elderly woman

Microscopical and Bacteriological Examination

The fluid which exuded from the affected muscles of the left thigh was found to be so rich in streptococci that it resembled a pure culture, sections of the muscle showed acute purulent myositis Acute inflammatory changes were present in a left inguinal lymph-node There was great engorgement of the sinusoids of the suprarenal glands, with focal cellular infiltration (mainly lymphocytic) No important abnormalities were seen in sections of spleen, liver, and kidney

Cultures from the affected muscles of the left thigh gave a profuse growth of hæmolytic streptococci of group A, type 3, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol Small numbers of the same kind of organism were found in the fluid from one of the bullæ near the left knee. A few hæmolytic streptococci were found in a swab taken at necropsy from the nares, but these were thought to be probably contaminants, no streptococci were found in an intranasal swab Cultures from the spleen were sterile

FOURTH CASE

A housewife, aged 72, complained of malaise on Feb 27, 1956, and next day she stayed in bed, feeling shivery On Feb 29 she sent for her doctor because she had a pain in her left upper limb, this pain was in the region of the shoulder and scapular region, and the patient regarded it as rheumatism, saying that she had had a lot of pain in her right shoulder for several months, but that it was now better Some years previously she had been treated for a rheumatic swelling in one hand

On examination her temperature was 101 2°F and pulse-rate 80, her left shoulder was not hot or swollen, but there was an irregularly shaped patch of erythema inside the left elbow The patient said that she had had a similar red patch on one arm a few weeks before.

Course and Treatment

Despite analgesics and a barbiturate tablet the pain in the left arm disturbed her sleep, and next morning (March 1) there was some swelling of the upper part of the arm, which was tender to touch and painful on movement She was transferred to a nursing-home because nursing facilities at home were inadequate, on admission at about 11 A M. her temperature was 99 2 F, pulse-rate 80, and respirations 28 In the evening her arm looked and felt the same, except that the patch of erythema was much paler Her colour was good, and she looked sleepy and quiet Nevertheless her nurse thought she appeared more ill than her temperature (99°F), pulse-rate (84), and respirations (24) suggested That night the patient slept at first, but at 2 A M her condition was very poor, and she seemed to have difficulty in swallowing, her temperature now was 103°F, pulse-rate 106, and respirations 38 Her condition continued to deteriorate, and about 4 30 A.M she became unconscious, with feeble pulse, and shallow respirations Nikethamide, oxygen, intramuscular penicillin (600,000 units), and intravenous saline solution and glucose did not revive her, and she died at 6 25 A M on March 2

Necropsy Findings

Acute streptococcal myositis of the left triceps brachii Swelling of left upper arm, with an area of brawny œdema on its posterior surface Numerous ill-defined abscesses in the pale-brown triceps muscle, pus in intermuscular septa and adjacent to the humerus No evidence of osteomyelitis in humerus after longitudinal bisection Left shoulder-joint and elbow-joint normal One superficial scratch (less than 1 cm long) on the skin of the metacarpo-phalangeal joint of left thumb, this appeared to be several days old and did not look inflamed Slightly enlarged and acutely inflamed lymph-nodes in left axilla No thrombus in normal left brachial vein and artery No hæmolytic staining of aorta or other blood-vessels Heart valves normal and free from vegetations, myocardium brown and flabby Diffluent pulp in small soft purple spleen Moderately severe congestion and œdema of lower and posterior parts of lungs Cloudy swelling of cortex of kidneys, with a few patches of hyperæmia just under the capsule. No pyæmic abscesses in the kidneys or in any other organs Scars of old tonsillectomy and partial thyroidectomy operations, thyroid gland represented by small remnants of lateral lobes only A well-nourished elderly woman

Microscopical and Bacteriological Examination

Smears from the pus in the left triceps muscle showed numerous gram-positive cocci in chains, and in sections of the muscle the picture was that of acute purulent myositis Acute inflammatory changes were seen in the left axillary lymph-nodes and the spleen, severe congestion, œdema, and intra-alveolar hæmorrhage in the lower lobe of the left lung, large-

This pain increased in severity and by the evening the limb was swollen

Next day (Oct 17) the pain was rather less severe, but she still felt unwell, and in the afternoon she was visited by her doctor, who found that her temperature was 103°F Arrangements were made for her to be admitted to hospital next day, but in the evening her relations noticed that she was becoming difficult to talk to and did not seem to know what was going on The doctor was called again and sent her to Addenbrooke's Hospital as an emergency She was admitted at 12 30 A M on Oct 18 restless, dyspnœic, cold, and sweating, with radial pulses barely perceptible and very rapid (rate about 140 a minute), blood-pressure 70/40 mm Hg, and temperature 102 6°F Her left thigh was œdematous and hot, the skin over it being cyanotic, with a patchy lividity Her urine contained albumin and acetone She was given penicillin and aureomycin intravenously, but within half an hour of admission she was unconscious and apparently moribund, and at 1 55 A M she died

Previous History

Since the age of 17 she had had occasional " running sores ", rather like small boils, which came out occasionally on all parts of her body For these she received a course of penicillin injections three years before her final illness After this she had only a few of these sores, and none recently For about ten years she had also at times had painful lumps which appeared near joints, especially on her hands and feet, and lasted a day or two She also had " a form of rheumatism ", with some stiffness of the limbs and joints

Necropsy Findings

Acute suppurative streptococcal myositis of the left quadriceps femoris muscle, which was pale and abnormally soft, with the individual fasciculi of muscle-fibres separated by thin greenish-yellow pus The purulent infiltration extended up to the groin and down to the knee Moderate œdema but no purulent infiltration of the left leg below the knee Moderate excess of turbid glairy brownish-pink fluid, probably containing inflammatory exudate, in the left knee-joint, with conspicuous hyperæmia of the synovia of the joint but no erosion of the articular cartilage Slight excess of almost clear glairy brownish-pink fluid in the otherwise normal left hip-joint Left femur, tibia, and fibula normal externally and on bisection, with no evidence of osteomyelitis No abnormality of adductor or hamstring muscles of left thigh

Hyperæmia of skin of inner aspect of left thigh above the middle, with several recent bullæ on the hyperæmic area These bullæ were not observed during life and must be regarded as agonal Several small pitted scars around both knees, and one on the back of the left thigh No recent septic lesions on skin of thigh or elsewhere, except the bullæ already mentioned No thrombosis of veins of left lower limb, although the femoral and popliteal vessels passed through purulent tissues

Considerable inflammatory enlargement of left inguinal and iliac lymph-nodes No hæmolytic staining of the lining of aorta or other blood-vessels Swollen ill-defined malpighian bodies in bright purple-red pulp of slightly enlarged spleen Blurred pattern in swollen suprarenal glands A few purple-red radial streaks, but no abscesses, in cortex of kidneys No pneumonia or abscesses in greatly congested lungs Tonsils absent Some cloudy swelling of myocardium, heart valves normal Cyanosis of fingers A well-nourished woman

Microscopical and Bacteriological Examination

The purulent exudate in the left thigh contained very numerous streptococci, the left inguinal lymph-nodes were acutely inflamed, and severe parenchymatous degeneration was seen in the kidneys, excessive leucopoiesis in the bone-marrow, and slight centrilobular large-droplet fatty change in the liver

Cultures from the affected muscles grew hæmolytic streptococci of group A, type 4, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol Two cultures from the spleen were examined, one was sterile, but the other yielded a few colonies of streptococci

SECOND CASE

A man, aged 33, by occupation a market trader, was admitted to Addenbrooke's Hospital on Oct 27, 1952, complaining of severe pain in his left thigh He said that the pain had begun the day before, it then prevented him from walking, and he had stayed in bed all day, sweating much

On admission he was distressed and sweating, with temperature 103 2°F, pulse-rate 132, respirations 20 a minute There was swelling and acute tenderness of the lower anterior part of the thigh, down to and including the patellar region, with erythema of the skin Examination of his blood showed hæmoglobin 16 2 g per 100 ml, leucocytes 23,000 per c mm (neutrophils 84% = 19,320 per c mm, juvenile forms 6% = 1380 per c mm, neutrophil myelocytes 0 5% = 115 per c mm)

Treatment and Course

The patient had been given an injection of penicillin before admission, and at 8 P M another was given (500,000 units) A blood-culture taken at 11 30 P M proved to be sterile Further injections of penicillin 500,000 units were given three hourly until his death on Oct 29 (total dosage 6,000,000 units) On Oct 28 he appeared very toxic and ill, his temperature was down to 98 4° F, but his pulse-rate remained 130

Operation —Under general anæsthesia an incision was made into the lateral aspect of his left thigh Pus was observed coming from the under-surface of the rectus femoris muscle, and much of this muscle and the vastus lateralis muscle appeared necrotic it did not bleed or contract No pus was found around the femur, which looked healthy Necrotic muscle was removed until healthy tissue appeared Thin watery purulent fluid oozed from the cut surface of the necrotic muscle, but no gas was seen, nor were there any localised abscesses The incision was closed with nylon sutures placed wide apart The patient was now given aureomycin 250 mg four-hourly, and later terramycin in an intravenous drip, but his condition steadily deteriorated, his pulse-rate rose to 200, and he died at 10 30 A M on Oct 29, apparently of extreme toxæmia

Necropsy Findings

Acute suppurative streptococcal myositis of left thigh Thin pinkish-red purulent fluid exuded from the partially necrotic remnants of the left vastus lateralis and rectus femoris muscles Similar exudate in fascial planes of the thigh from popliteal fossa almost to the groin Surgical incision on lateral aspect of the left thigh Adductor and hamstring muscles of left thigh almost normal in appearance Left femur and hip- and knee-joints normal Acute inflammatory swelling of left inguinal lymph-nodes Slight general enlargement of lymph-nodes Very soft purple-grey acute septic spleen Pale red brown myocardium and normal heart valves Congestion and œdema of heavy dark purple-red lungs Pale yellow patches on surface of swollen yellow-brown liver The capsules stripped easily from the surfaces of the pale kidneys No pyæmic abscesses found in any organ A well-nourished young man

Microscopical and Bacteriological Examination

Acute purulent myositis of the left thigh Gram-positive cocci were abundant in some parts of the section, but many appeared degenerate and had lost their gram-positive staining, many had been phagocytosed by leucocytes Severe acute inflammatory changes were present in the spleen, but no bacteria were seen in a gram-stained preparation Numerous leucocytes were crowded in the sinusoids in some parts of the liver Parenchymatous degeneration of kidneys Congestion, hæmorrhages, and œdema of lungs

Cultures of the purulent fluid from the left thigh muscles (operation specimen) gave a profuse growth of hæmolytic streptococci of group A, type 3, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol Nose and throat swabs were taken on Oct 31 from each of the four members of the patient's household No hæmolytic streptococci were isolated from any of these swabs

THIRD CASE

A housewife, aged 76, was admitted to Addenbrooke's Hospital on May 24, 1953. She was too ill and confused to give a history, but according to her relatives her illness had begun five days previously, when she had complained of pain in her face, for this she had applied a liniment. Next day she had pain in her left thigh and aching in all joints, a red patch "as big as a tennis ball" appeared on the outer aspect of her left thigh. Her nose was now swollen, and a scab formed on it. Two days later (two days before admission) she seemed very ill, her breathing was "very heavy" and her lips and cheeks looked blue, but she was said not to have been febrile. Malaise and general weakness continued, and the day before admission she fell down while walking to the lavatory.

On examination she was extremely ill, with signs of peripheral circulatory failure. Her nose, ears, and extremities were deeply cyanosed and her features pallid. Her temperature was 100°F and systolic blood-pressure 55 mm. Hg, the diastolic pressure could not be recorded, the pulse was of poor volume (rate 140). A scabbed lesion about 2 cm. in diameter was present on her nose. Her left leg was swollen, especially the thigh, which was very tender on its lateral aspect. All movements of this limb were very painful, it was held externally rotated. In view of the history of a fall, the possibility of a fracture of the neck of the left femur was considered, but the first need obviously was for treatment of the profound circulatory failure, which was thought possibly to be due to septicæmia, to pulmonary embolism, or to myocardial infarction. Treatment with intravenous infusions, 'Eucortone', penicillin (500,000 units), and nikethamide was, however, of no avail, and the patient died in coma about seven hours after admission.

Previous History

Rickets in childhood, and winter cough and "rheumatism" for years.

Necropsy Findings

Acute streptococcal myositis of the left thigh. Thin yellow-pink fluid exuded from the pale grey-pink cut surfaces of the vastus lateralis and adjacent muscles of the left thigh, there was one moderately well-defined abscess (1.5 cm. in diameter) containing thick creamy-yellow pus deep in the substance of the vastus lateralis muscle, with several smaller abscesses near it. No thrombosis or other abnormality of the veins of the left lower limb. Left femur, knee-joint, and hip-joint normal. Several superficial bullæ (largest 4 × 2 cm.) containing clear reddish fluid on skin of posterolateral aspects of left thigh just above the knee. No septic lesions of any kind on the rest of the skin of the left leg, the search particularly included the clefts between the toes. Rather soft and pale normal-sized spleen (125 g.). No hæmolytic staining of aorta or other blood-vessels. Moderately severe atheroma of coronary arteries, with narrowing and calcification. Rather flabby brownish-red myocardium. Heart valves functionally normal and devoid of vegetations. Congestion and bullous emphysema of rather small lungs. Patchy centrilobular congestion in pale liver. Blurred pattern on cut surfaces of suprarenal glands (acute inflammatory swelling). One dry crusted lesion (2 cm. in diameter) on the left side of the nose. Mild osteoarthritic changes and Heberden's nodes in both hands. A moderately well-nourished elderly woman.

Microscopical and Bacteriological Examination

The fluid which exuded from the affected muscles of the left thigh was found to be so rich in streptococci that it resembled a pure culture, sections of the muscle showed acute purulent myositis. Acute inflammatory changes were present in a left inguinal lymph-node. There was great engorgement of the sinusoids of the suprarenal glands, with focal cellular infiltration (mainly lymphocytic). No important abnormalities were seen in sections of spleen, liver, and kidney.

Cultures from the affected muscles of the left thigh gave a profuse growth of hæmolytic streptococci of group A, type 3, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol. Small numbers of the same kind of organism were found in the fluid from one of the bullæ near the left knee. A few hæmolytic streptococci were found in a swab taken at necropsy from the nares, but these were thought to be probably contaminants, no streptococci were found in an intranasal swab. Cultures from the spleen were sterile.

FOURTH CASE

A housewife, aged 72, complained of malaise on Feb. 27, 1956, and next day she stayed in bed, feeling shivery. On Feb. 29 she sent for her doctor because she had a pain in her left upper limb, this pain was in the region of the shoulder and scapular region, and the patient regarded it as rheumatism, saying that she had had a lot of pain in her right shoulder for several months, but that it was now better. Some years previously she had been treated for a rheumatic swelling in one hand.

On examination her temperature was 101.2°F and pulse-rate 80, her left shoulder was not hot or swollen, but there was an irregularly shaped patch of erythema inside the left elbow. The patient said that she had had a similar red patch on one arm a few weeks before.

Course and Treatment

Despite analgesics and a barbiturate tablet the pain in the left arm disturbed her sleep, and next morning (March 1) there was some swelling of the upper part of the arm, which was tender to touch and painful on movement. She was transferred to a nursing-home because nursing facilities at home were inadequate, on admission at about 11 A.M. her temperature was 99.2°F, pulse-rate 80, and respirations 28. In the evening her arm looked and felt the same, except that the patch of erythema was much paler. Her colour was good, and she looked sleepy and quiet. Nevertheless her nurse thought she appeared more ill than her temperature (99°F), pulse-rate (84), and respirations (24) suggested. That night the patient slept at first, but at 2 A.M. her condition was very poor, and she seemed to have difficulty in swallowing, her temperature now was 103°F, pulse-rate 106, and respirations 38. Her condition continued to deteriorate, and about 4.30 A.M. she became unconscious, with feeble pulse, and shallow respirations. Nikethamide, oxygen, intramuscular penicillin (600,000 units), and intravenous saline solution and glucose did not revive her, and she died at 6.25 A.M. on March 2.

Necropsy Findings

Acute streptococcal myositis of the left triceps brachii. Swelling of left upper arm, with an area of brawny œdema on its posterior surface. Numerous ill-defined abscesses in the pale-brown triceps muscle, pus in intermuscular septa and adjacent to the humerus. No evidence of osteomyelitis in humerus after longitudinal bisection. Left shoulder-joint and elbow-joint normal. One superficial scratch (less than 1 cm. long) on the skin of the metacarpo-phalangeal joint of left thumb, this appeared to be several days old and did not look inflamed. Slightly enlarged and acutely inflamed lymph-nodes in left axilla. No thrombus in normal left brachial vein and artery. No hæmolytic staining of aorta or other blood-vessels. Heart valves normal and free from vegetations, myocardium brown and flabby. Diffluent pulp in small soft purple spleen. Moderately severe congestion and œdema of lower and posterior parts of lungs. Cloudy swelling of cortex of kidneys, with a few patches of hyperæmia just under the capsule. No pyæmic abscesses in the kidneys or in any other organs. Scars of old tonsillectomy and partial thyroidectomy operations, thyroid gland represented by small remnants of lateral lobes only. A well-nourished elderly woman.

Microscopical and Bacteriological Examination

Smears from the pus in the left triceps muscle showed numerous gram-positive cocci in chains, and in sections of the muscle the picture was that of acute purulent myositis. Acute inflammatory changes were seen in the left axillary lymph-nodes and the spleen, severe congestion, œdema, and intra-alveolar hæmorrhage in the lower lobe of the left lung, large-droplet fatty change of moderate degree in the liver, severe degenerative changes in the cortex of the kidneys, and benign hypertensive changes of moderate degree in the arteries and arterioles of the kidneys and suprarenal glands

Cultures from the pus in the triceps muscle gave a profuse growth of hæmolytic streptococci of group A, type 12, which were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol Cultures from the spleen were sterile

Discussion

These four examples of spontaneous streptococcal myositis were acute febrile illnesses associated with pain and swelling in the muscles of a limb, leading to profound toxæmia with rapid feeble pulse, circulatory collapse, and death The patient may be young or old the pain may begin before or shortly after the constitutional disturbances In none of our four patients was the existence of septicæmia proved, unless the few colonies of streptococci obtained from one of the two cultures of the spleen of case 1 at necropsy is held to provide such proof In none of these cases, however, was blood-culture undertaken before antibiotic therapy was instituted, and in all probability general dissemination would have taken place before death if the patients had not been given such therapy Nevertheless, the myositis cannot reasonably be regarded as merely an incident in the course of a streptococcal septicæmia

Published reports of such cases as these are few, if one excludes the tropical cases already mentioned (Manson-Bahr 1954)

Payne (1881) described a case of acute myositis of the thigh of a woman aged 33, but, since the illness began during the puerperium and there is no note of the state of the veins at necropsy, the possibility of septic thrombophlebitis cannot be excluded

Clark (1887) described a more definite case in a man aged 29, but neither in this case nor in that of Payne were the causal organisms identified, so they may not have been streptococci

Abram (1904) recognised streptococci as a cause of suppurative myositis and described two cases involving a pectoralis major muscle, these patients both recovered after surgical incision

Abrami and Worms (1930) described two cases, one involving the muscles of the shoulder region of a man aged 30, the other the thigh of a man aged 38, who also had streptococcal arthritis of a knee-joint In the former case streptococci were cultured from the blood These workers remark that such cases are rare and that " la myosite streptococcémique suraigue représente une entite nouvelle "

Traumatic streptococcal myositis, usually due to anærobic streptococci, was described by MacLennan (1943a and b, 1944), but this is in many ways different from the spontaneous myositis due to aerobic streptococci in the present cases The following case more closely resembles those of MacLennan, but the infecting organisms were aerobic streptococci of group A

FIFTH CASE

A man, aged 75, sustained a fracture of the neck of his right femur on Sept 23, 1952, and at operation next day the femoral head was removed and a Judet prosthesis fitted Prophylactic penicillin therapy was given from the first to the tenth day after operation (total dosage 13,500,000 units) The patient was found to have purulent bronchitis and emphysema On the sixth and seventh postoperative days there was a very slight rise of temperature (maximum 99 F), otherwise he was apyrexial He was discharged on Oct 13 On Nov 15 he was found dead, lying on the floor near the bed at his home

Necropsy Findings

The right hip-joint contained milky-grey pus, and a large abscess cavity (12 × 14 cm) was present in the right buttock The abscess communicated with the hip-joint through a large aperture in the posterior part of the capsule The arthroplasty incision was completely healed, and there was no external evidence of infection Except for some acute bronchitis and bronchiolitis in the lower lobes of the lungs, no important abnormalities were found elsewhere in the body, and death was attributed to the arthritis and buttock abscess

Bacteriology

The pus contained hæmolytic streptococci of group A, type 11/27/44 Cultures from the spleen yielded a profuse growth of the same organisms, these were fully sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol

The streptococci may have gained access to the hip-joint at the operation and been suppressed but not exterminated by the subsequent antibiotic therapy, only to multiply when this was stopped The possibility of *hæmatogenous infection of a hæmatoma cannot, however,* be excluded

In the cases of spontaneous myositis (cases 1–4) the infection probably reached the muscle via the blood stream, because in none of the cases was there any history of a recent penetrating wound or of any intramuscular injection The portal of entry of the infection into the body remains obscure

The possibility of acute streptococcal myositis should be considered if a febrile patient complains of acute pain and tenderness of the proximal part of one limb, and on examination is found to have definite swelling of a muscular part of the limb, perhaps accompanied by a patch of skin erythema which may not immediately overlie the site of greatest pain and swelling

Unfamiliarity with the condition is the greatest obstacle to its diagnosis

Acute thrombophlebitis may be suspected, but the absence of œdema of the distal part of the limb and the absence of engorgement of the superficial veins speak against it In *acute osteomyelitis* the swelling is usually nearer to the end of a long bone, and the patient is likely to be younger The distinction between myositis and cellulitis may be difficult but is probably not of great practical importance Sudden development of profound toxæmia is one of the distinctive features of myositis Failure to recognise the onset of this toxæmia may have serious consequences The patient's temperature is unreliable as an index of his progress because it may fall as the toxæmia develops, and this may erroneously suggest improvement The continued rise in the pulse-rate and the general deterioration of the patient's condition should, however, reveal the true state of affairs

Streptococcal infections are now apt to be regarded too lightly As the cases here reported illustrate, the dangers of such infections are by no means past, and early diagnosis is of great importance Streptococci are sensitive to most antibiotics and very rarely become resistant, consequently antibiotic therapy may be expected to have excellent results if it is instituted early On the other hand, even the most massive antibiotic therapy may prove unavailing when severe toxæmia has already developed

Summary

Acute streptococcal myositis was fatal in 4 patients The thigh muscles were involved in 3 and the triceps brachii in the other

The portal of entry of the streptococci was not established

This infection can be fulminating, and early diagnosis and early antibiotic therapy are essential

We are indebted to Dr L C Martin, Mr B M Truscott, Mr T J Fairbank, and Dr A Kekwick for the use of their clinical records, and to Dr J Boissard, Dr R M Fry, and Dr M H Gleeson

White for the bacteriological investigations The necropsies on cases 1, 3, 4, and 5 were done on the instructions of H M Coroner for the City of Cambridge, who has kindly given us permission to publish our findings

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DERMATITIS CAUSED BY PENICILLIN IN MILK

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The incidence of sensitivity to penicillin is probably about 5% for the general population and 12–15% for those engaged in its manufacture or who have multiple allergies (Brown 1948, Boger et al 1953, Feinberg and Feinberg 1956, Frome 1957)

The first cases of contact dermatitis due to penicillin were in people exposed during its manufacture Many cases were later seen in nurses and in patients who had been treated with penicillin in contact with the skin for long periods (Pyle and Rattner 1944, Michie and Bailie 1945, Vickers 1946)

Since the introduction of machine milking, the incidence of mastitis in cows has increased, and the common practice among herdsmen is to inject 100,000 units of procaine penicillin into the teat of the infected quarter 70% of cases are due to *Streptococcus agalactiæ*—an organism highly sensitive to penicillin—and the infection rapidly subsides (Milton 1950) As a result of this treatment, milk may contain penicillin, and this has already given rise to anxiety in the United States (McLean 1956, Welch 1957) If patients previously sensitised to penicillin by local application drink milk containing penicillin, dermatitis may develop and persist indefinitely if its true nature is not recognised

We have recently seen two patients in whom penicillin in milk seems to have been the cause of dermatitis

Case-reports

Case 1 —A woman, aged 55, gave a long history of skin trouble, starting with eczema in infancy At the age of 20 dermatitis of the neck developed owing to contact with brown dyed fur When aged 33, she had dermatitis of the suspender areas

At the age of 45 a rash then developed on her ears after contact with a pig with scaling ears, treatment with penicillin resulted in severe dermatitis of the ears, and the rash spread to the face and neck

At the age of 49, a rash had developed on her hands while she was working in a plant nursery Allergy tests, in hospital, were all negative After fourteen weeks in hospital she improved, but thereafter she had recurrent attacks of dermatitis affecting particularly the face and hands

A further attack started in April, 1957, (when the patient was aged 55) and she had an acute exacerbation two days before coming to the outpatient department in August She then had acute dermatitis, with erythema and weeping, of the whole of her face, neck, and the backs of the hands and forearms

Investigation

The patient was admitted to hospital with a diagnosis of acute contact dermatitis The condition slowly improved She was patch-tested to the following suspected contacts penicillin 200,000 units per ml, 2% nickel sulphate, English yew, tulip, Douglas fir, Lawson cypress, macrocarpa cypress, chrysanthemum, cineraria, lupin, tomato, strawberry leaf, raspberry leaf, carnation, antirrhinum, phlox, wallflower, privet, ivy, sweet-william, foxglove, and primula She gave strongly positive reactions to penicillin, primula, and nickel sulphate Other patches were negative

A more detailed history revealed that the patient had lived on farms for many years In 1956, when she had her own cow, which had not had penicillin, she was well, but when the cow stopped lactating and she had fresh bulked milk, probably containing penicillin, she had a relapse Her previous attacks had been associated with drinking about a litre of fresh bulked farm milk daily She improved when away from the farm

Desensitisation

It was decided to desensitise the patient to penicillin She gave no reaction to 2 units, but 4 units intramuscularly produced an exacerbation of the dermatitis on the previously affected areas The dose was then reduced to 1 unit, and to avoid penicillin-contaminated milk she was given goat's milk On these small doses of penicillin she had much irritation, and some of the injections were followed by nausea With perseverance, however, the daily dose was increased so that she now tolerates 1,000,000 units, and the dermatitis has cleared She has returned to drinking cow's milk with no ill-effects

Analysis of fresh milk from the farm where she lived showed a penicillin content of 4 units per ml

Case 2 —A man, aged 44, was admitted to hospital on Sept 27, 1957 He has a small mixed farm, with 14 cows milked by machine Ten days before admission he had an attack of lumbago Five days later a rash developed round the genital and pubic region, which was treated with 'Caladryl' The day before admission the rash became generalised and was accompanied by fever (101° F), palpable painful glands in the groins and axillæ, and swelling of the knees and ankles Twenty years ago he had a transient rash on the arms and abdomen, and eighteen months ago a similar rash on the back

On examination he had severe erythema of the whole skin On the trunk and thighs there were small tightly packed vesicles, many of which contained turbid fluid There was much swelling of the lower legs, and the lymph-glands in the neck, axillæ, and groins were palpable and tender

Acute epidermal sensitisation, probably due to a drug, was diagnosed On being questioned further, the patient said that he had been giving his cows penicillin for mastitis for two years He had started to treat one with procaine penicillin (100,000 units into each quarter) ten days previously Milk from this cow had been added to the rest of the farm milk, which he had been drinking

He was treated with prednisolone, because the reaction was severe, it rapidly subsided Patch tests were positive to procaine penicillin 100,000 units per ml and negative to caladryl

Discussion

Welch et al (1955) found penicillin, in concentrations of 0 003–0 08 units per ml, in 11 6% of 474 samples of milk examined from sixteen States in America The maximum quantity was thus about 20 units per glass Moreover, penicillin could be detected in the milk six days after treatment, though most had been excreted after three days

In a later survey the same workers (Welch et al 1956) found penicillin in a concentration of 0·003–0 550 units per ml of milk in 5 9% of 170 samples The American

Food and Drug administration has ruled that milk from any cow which has been treated with penicillin should be discarded for seventy-two hours It seems, however, that this order is not universally observed, and sometimes penicillin may even have been added to milk as a preservative Penicillin in milk is well recognised as a cause of urticaria in America (Welch 1957), but we have been unable to find any records of its being responsible for the reactivation of dermatitis in patients previously sensitised

In Britain there is a rather indefinite ruling that milk from infected cattle shall not be distributed Since mastitis can often be diagnosed early and penicillin produces in most cases a rapid cure within hours, most of the milk from mildly infected cattle is distributed in the normal way

Berridge (1956) found over 0 01 units of penicillin per ml of bulked milk in 4 9–47% of a large number of samples from eight districts in England and Wales In some samples the concentration of penicillin reached 0 8 units per ml of milk For single producers, 0 036 units or more per ml was found in 1 4–4 8% of samples from seven districts, and 0 01 units or more in 4 2–18 5% of samples There seemed to be no seasonal variation

Naturally those living on dairy farms, like the two patients described here, will be more liable to a high penicillin intake than the general population, which benefits from more extended bulking with consequent dilution of the penicillin content Our first patient drank nearly a litre of milk daily As milk from her farm contained 4 units of penicillin per ml she may have ingested 4000 units of penicillin daily She was sensitive to 4 units of crystalline penicillin G intramuscularly

The blood content after injection of 4 units would be about 0 000013 units per ml (Florey 1952) Bierlin (1956) described a penicillin-sensitive patient who reacted severely to an injection of 0 000003 units of the drug Salk poliomyelitis vaccine contains 0 5 units of penicillin per ml (Siegal 1955) and has produced reactions observed in this hospital and in the United States (Clyde 1956) Carter and Cope (1954) reported a severe constitutional reaction to the topical application of penicillin eye ointment, and Madali (1954) reported a severe reaction to a penicillin lozenge one minute after it had been placed in the mouth

The incrimination of penicillin is beyond doubt in both the cases reported here Many chronic skin lesions of obscure origin may in fact be kept active by the daily ingestion of penicillin-contaminated milk It seems that the penicillin content of bulked milk is so low as to be innocuous to normal persons, but not to the sensitive

The number of persons sensitive to penicillin increases with the more widespread use of the drug Accordingly it is important that this country should adopt the American ruling prohibiting the distribution of milk for seventy-two hours after the treatment of mastitis

Summary

Two cases are reported of allergic dermatitis due to penicillin in milk from cows treated for mastitis

One sample of milk tested contained 4 units of penicillin per ml

It is suggested that the American ruling prohibiting the sale of milk from cattle for seventy-two hours after the last injection of penicillin should be adopted in Britain

We thank Dr W H H Jebb and Mr A H Tomlinson, of the Public Health Laboratory, Oxford, for the estimations of penicillin in milk

References at foot of next column

FATE OF ORLON AORTIC IMPLANT IN MAN

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Since successful aortic grafting with cloth tubes was first reported (Blakemore and Voorhees 1954, Shumacker and King 1954) this method has proved its worth in many patients So far no observations seem to have been made on the way in which such material is finally accommodated in the human aorta, most of the published data concern experimental operations on the dog, and specimens recovered from patients who died soon after operation We describe here our findings in a patient who died two and a quarter years after the insertion of an abdominal aortic graft of 'Orlon' cloth

Case-report

A man, aged 63, with pulmonary tuberculosis began to have nausea and abdominal pain soon after the first administration of streptomycin and p-aminosalicylic acid Examination by Dr G Shneerson revealed an abdominal mass which he diagnosed as an aortic aneurysm The pain increased, and on Feb 16, 1955, we explored the abdomen and resected a large aneurysm which involved the aorta from 3–4 cm below the renal arteries to the first part of the common iliac arteries This gap was restored by means of a graft of orlon cloth previously prepared in the form of a bifurcation The graft fitted well at the upper end, but the iliac branches were rather narrower than the corresponding ends of the patient's somewhat dilated iliac arteries, the cuffs of the branches were turned down, reducing this disproportion but requiring the suture of only a single layer of cloth at the two lower anastomoses, instead of the double fold preferred The patient recovered well and experienced no further pain, but he was still unable to tolerate chemotherapy, and the tuberculosis progressed On May 27, 1957, two and a quarter years after the operation, he died during a hæmoptysis

Postmortem Appearance

The external appearance of the specimen recovered at necropsy suggested that it consisted simply of most of the abdominal aorta and the first parts of the common iliac arteries, with the stumps of the cœliac, mesenteric and renal arteries and the related parts of the corresponding veins (fig 1) The upper cut end was 2 5 cm (1 in) above the cœliac axis, the right common iliac artery was about 6 cm long, while the left was about 3 cm long and was noticeably wider than the right When the specimen was cut down its left lateral border and

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opened out, the orlon graft was immediately revealed, the weave of the fabric being only partly obscured by patches of fibrin The graft had replaced the excised arteries from a line 4 cm below the renal arteries down to lines 1 5 cm beyond the origins of the common iliac arteries There was considerable atheroma, especially of the common iliac arteries, the right was of about normal calibre, but the left was dilated and measured 2 × 1 cm in cross-section The following striking features call for comment

(1) Fibrin had been deposited on the internal aspect of the orlon only in patches The patches were irregular in outline and did not exceed 0 5 mm in thickness, and large areas of the orlon appeared completely bare

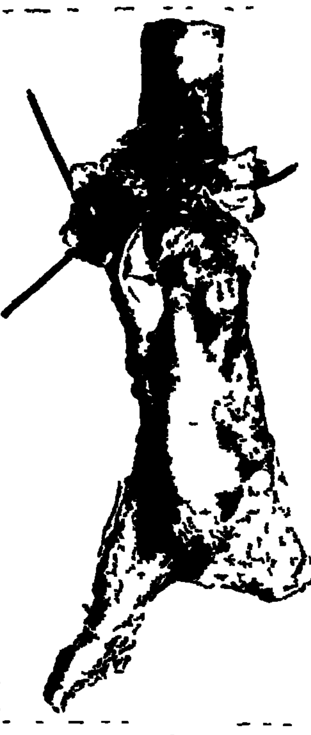

Fig 1—Specimen from front Dark rods show positions of inferior vena cava and right and left renal veins

(2) The external aspect of the orlon was not attached to the surrounding tissues except at the anastomoses and down the sides, where there were seams joining the anterior and posterior halves of the graft At other places the orlon either was absolutely loose or could be easily detached from the surrounding tissues, leaving an imprint of its mesh on the tissue surface with which it had been in contact

(3) There were transverse wrinkles in the orlon at some places—notably near the upper anastomosis posteriorly, a little lower down anteriorly, and just above the iliac anastomoses In the last-named situation the wrinkles made a much larger proportional reduction of the lumen than in the aorta, but there was no evidence that the wrinkles had affected the site or increased the likelihood of fibrin formation

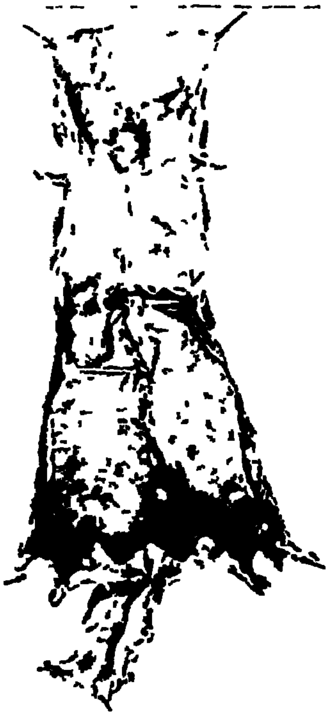

Fig 2—Complete specimen opened out after cutting down its left border Note detachment of orlon (at right lower corner)

(4) At the right side of the graft, near its upper end, a free edge of the orlon, showing the dentate outline caused by pinking shears, had been inadvertently turned in and was protruding into the lumen Here again there was no increase of fibrin formation

(5) The tissue around the graft was dense pale grey connective tissue, for the most part measuring less than 1 5 mm in thickness

These features can be observed in figs 2 and 3

Strips of the orlon and related connective tissue were taken from the front and back of the graft, including one of the seams Sections were prepared for histological examination, from which the following points emerge

(1) The tissue covering the orlon exteriorly is dense collagenous fibrous tissue, almost avascular, with few fibrocytes and very few, if any, elastic fibres A thin layer of fibrin-like material is interposed at some places between the fibrous tissue and the orlon, but there is no other indication that the orlon has any irritative or “ productive ” effect on contiguous tissues The dense connective tissue around the graft was probably formed by organisation of fibrin laid down at the time of insertion of the graft or soon after

(2) There is no colonisation or infiltration of the orlon by fibroblasts or histiocytes The only place where anything resembling this was observed was on the exposed aspect of the lateral seams, but it is not truly a matter of infiltration but of enclosure

(3) Very little foreign-body giant-cell reaction was observed Again the seams are the exception, and again appearances are deceptive, for the reaction is in fact most pronounced in relation to the thread used in stitching the seams This thread, which was nylon, can be distinguished partly by its orientation and partly by its being more strongly anisotropic than the orlon

(4) The fibrin adhering in places to the orlon has in its meshes only polymorphs and a few red cells There is no sign of endothelialisation

Comment

Very little is known about the long-term results of putting plastic grafts into the human body, but those that survive the operation and its immediate complications appear to do very well Experimental operations in dogs (Voorhees et al 1952) have indicated that such grafts become permeated, lined, and surrounded by fibrous tissue Hufnagel (1955), dealing with orlon grafts, says

“ The inner surface becomes covered with fibrinoid material gradually islands of endothelial like cells appear on the surface, this process then continues with coalescence of these areas to form a layer within the orlon, and a fibrous layer outside it Some fibres appear to grow through the spaces in the orlon cloth although these are quite fine and tenuous in character ”

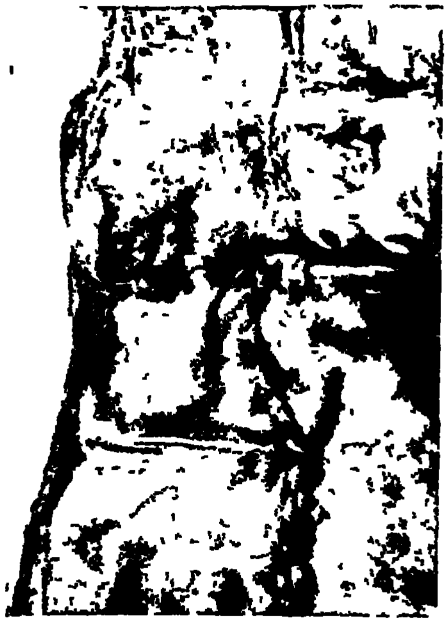

Fig 3—Interior of orlon graft and anastomosis with abdominal aorta Note mesh of cloth, obscured by patches of fibrin (e g., top right)

In the present case a very different condition is found Scar tissue has been formed only *outside* the graft, the cloth itself seems to have been almost inert to the host cells and tissues “ Foreign body reaction ” towards the fabric has been negligible, nor has the orlon aroused much fibrin formation, yet there has been no leakage through any part of it Wrinkles and other faults in the preparation and insertion of the graft do not seem to have mattered In some ways this inert behaviour reflects that of the arterial homograft in man Rob (1954) reported only very incomplete active invasion and practically no lining by host cells in several homografts in man exhibited some months after implantation

The findings in this case are so surprising that some peculiarity of the patient or his treatment may be suspected This question can be settled by future findings in other patients with orlon grafts or with grafts of another cloth such as 'Terylene'

We are indebted to Dr John Taubman for recovering the graft at necropsy

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FULMINATING BERIBERI

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BERIBERI is very rare in Great Britain, only 13 deaths from it were recorded in this country over the five-year period 1949–53 Fulminating beriberi is almost unknown in Great Britain

Yudkin (1938) described a young Indian who developed anorexia, dyspnœa, malaise, œdema, palpitations, and tachycardia after living in London for eight months on a diet of polished rice This patient, and others with cardiovascular disease, responded to large doses of aneurine (vitamin B_1) (Price 1938, Jones and Bramwell 1939, Ungley 1939, Konstam and Sinclair 1940, Bates 1941, Paulley and Aitken 1944, Thomson and Keay 1952) Fatal cases were reported by Wood (1939), and by Allibone and Baar (1946)

Only in the past fifteen years has it been generally recognised that beriberi may present not only as the well-known syndrome of œdema, heart-failure, and peripheral neuropathy, but also with cerebral manifestations—the long-recognised syndromes of Wernicke's encephalopathy and Korsakow psychosis We describe here a case of fulminating beriberi showing all five possible manifestations of aneurine deficiency—namely, peripheral neuropathy, heart-failure and œdema, Wernicke's encephalopathy, and Korsakow psychosis —a combination not, we believe, previously reported in Britain

Case-report

A woman, aged 55, was admitted to the neurosurgical department of the Royal Northern Hospital on July 27, 1955, for investigation of her complaint of weakness of the legs She had been quite well until May 28, when she felt faint, and collapsed on the floor and hit her head After resting in bed for a month she was well apart from an occasional bout of vomiting, headache, and giddiness, but when she tried to stand again her legs collapsed under her Her relations noticed that she was sometimes drowsy and confused Her doctor found a motor ataxia and bilateral nystagmus, suspected a subdural hæmatoma or a cerebellar tumour, and referred her for a neurosurgical opinion

The patient was thin weighing 7 st There was some loss of memory for recent events including the actual fall She walked with difficulty All her limbs were wasted, and there was fasciculation of the muscles, but their tone and power were normal except for bilateral weakness of ankle dorsiflexion All tendon reflexes were absent, but the plantar responses were normal No abnormal physical signs were found in the sensory system, the cranial nerves, or any other system of the body She had had no other serious illnesses She lived alone and did part-time work as a railway toilet attendant Both she and her relations maintained that her diet was full, and that she drank an occasional glass of beer only

Investigations

Peripheral neuropathy was diagnosed, and the underlying cause was investigated Radiographs of the skull and chest, the blood-count, and the cerebrospinal fluid were normal The Wassermann and Kahn reactions were negative There was histamine-fast achlorhydria In the sternal marrow there was no evidence of megaloblastic erythropoiesis Electromyography of the arm and leg muscles showed fibrillation with some decrease in the pattern of motor activity on voluntary movement Conduction in all the long nerves in the arms and legs was normal These findings supported the diagnosis of peripheral neuropathy

Course

With the aid of physiotherapy the patient's walking improved, but on Aug 21 she suddenly became unwell, losing her appetite and vomiting her meals By Aug 23 she was apathetic and apprehensive, her tongue was smooth and pale, and her calves were very tender Next day she became frightened, disoriented, and confused, with delirium and hallucinations, she lay listlessly curled up in bed, and refused to eat Retention of urine developed and she had to be catheterised

On the morning of Aug 25 the patient rapidly lapsed into stupor She was motionless, and sacral and ankle bedsores had developed She could not move her eyes downwards or laterally, and there was divergent strabismus with disconjugate wandering and failure of convergence Her fundi were normal There was mild intention tremor Wernicke's encephalopathy with peripheral neuropathy, due to avitaminosis, was diagnosed She was at once treated with vitamins B and C by injection of 7 ml high-potency 'Parentrovite' * twice daily for seven days, followed by the maintenance preparation, in addition cyanocobalamin (vitamin B_{12}) was injected—1 mg daily at first, and then 100 µg daily

Next day ascites appeared, with œdema of the sacrum and legs, tachycardia, and a raised jugular venous pressure, but she was more alert and could conduct a simple conversation The diagnosis was now established as beriberi She was given a high-calorie and high-protein diet through a Ryle's tube

Progress Under Treatment

The signs of heart-failure had disappeared by Aug 30, when convergence and downward movement of the eyes had recovered The paralysis of lateral movement lasted for two days only, and was then followed by nystagmus This was at first produced by small deviations of the eyes, and then gradually improved to appear only at the extreme range of lateral movement There was transient right facial paresis and ptosis on Aug 28 Soon the patient became cheerful and voluble and began to read the newspapers again, but her amnesia for the recent past was complete and she confabulated freely (Korsakow's psychosis) She continued to have delusions and hallucinations, but the vomiting stopped, she took a large solid diet, and gradually walked unaided

On Oct 8 she had numbness, pins and needles, and cramp in the hands, and a few days later similar sensations in her legs Her calves were only slightly tender On Nov 3 her ankles became swollen again, and œdema increased in the following week On Nov 11 she became suddenly breathless, with precordial pain and anxiety The pulse-rate was 120 a minute The apex-beat was six inches from the midline in the seventh intercostal space The jugular venous pulse was at the angle of the jaw and the abdomen swollen Treatment with oxygen [illegible] brought about [illegible] rate was 80 a [illegible] pressure were [illegible] ascites

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* Parentrovite (high potency) contains in each 7 ml Aneurine hydrochloride 250 mg nicotinamide 160 mg, riboflavine 4 mg, calcium pantothenate 5 mg pyridoxine hydrochloride 50 mg, and ascorbic acid 500 mg The maintenance preparation contains 100 mg of aneurine, but is otherwise identical

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A PORTABLE URINAL

purpose of the apparatus is to allow patients with incontinence or nocturnal enuresis the comfort of a por- rinal that may be worn by day and by night It is for ambulant or recumbent male or female patients - nsists of a thin waterproof bag worn under the perineum ween the thighs The bag is divided into two chambers,

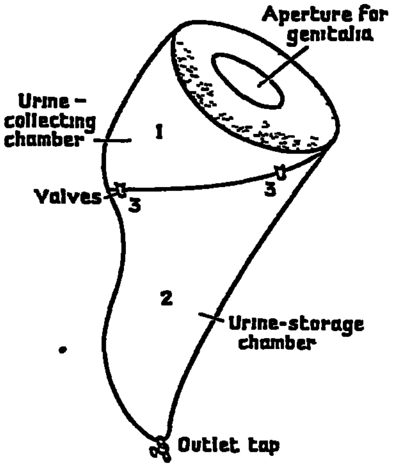

Fig 1

collects the urine (1, see figure) The second is larger eives all the urine from the first chamber (2) For patients the top of the bag is made concave to fit the or male patients the hole in the top is large enough for talia to be inserted into the first compartment. revent the urine from spilling backwards and over- , non-return valves (3) are situated between the rs The valves are placed anteriorly and posteriorly in separating these chambers This allows the patient to ny posture without inconvenience or risk of leakage

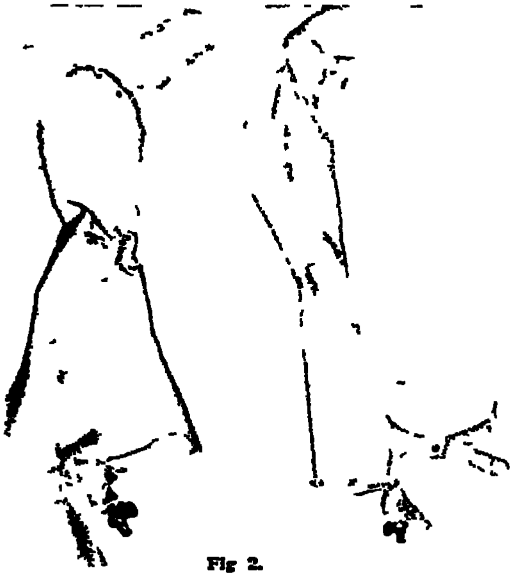

Fig 2.

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FATE OF 240 REPORTED CASES (1881–1951) OF WERNICKE'S ENCEPHALOPATHY IN RELATION TO TREATMENT WITH PARENTERAL ANEURINE

—	Survived	Died	Total
Treated	58 (*69%*)	26 (*31%*)	84
Untreated	10 (*6%*)	146 (*94%*)	156
All	68 (*28%*)	172 (*72%*)	240

is not an absolute figure but varies with the carbohydrate content of the food, being about 2 mg for an ordinary 3000 calorie diet This vitamin content in mg of aneurine (A) can be expressed as a ratio per thousand non-fat calories (N F C) Studies of human aneurine deficiency, both experimental and natural, show that where this ratio A /N F C falls below 0 3, symptoms of deficiency appear (Williams and Spies 1938)

30,000 men were suddenly changed from a normal to an aneurine-deficient rice diet when Singapore was captured in 1942 Wernicke's encephalopathy appeared among British prisoners after six weeks, when the A /N F C ratio was about 0 194 Of de Wardener and Lennox's 52 cases, 45 had dysentery or diarrhœa as a precipitating factor With improvement in the diet there were no further cases In the months before the liberation in August, 1945, the ratio A /N F C was just above the critical 0 3 After the liberation the diet was suddenly supplemented by rice and protein, the A /N F C fell to 0 204, and a beriberi outbreak appeared within fourteen days (Pantridge 1946)

Barrie (1947) was the first to emphasise the danger of the routine hospital diet (? high calorie, low aneurine) to patients with aneurine deficiency He reported that 3 patients who had vomited for months or years from gastric disease died of Wernicke's encephalopathy after being admitted to hospital Perhaps our own patient is another example of a few weeks of a hospital diet suddenly increasing the denominator, and thus lowering the ratio A /N F C , and precipitating the acute deficiency state of Wernicke's encephalopathy

It is not clearly understood how gastric atrophy produces the secondary deficiency of aneurine, a vitamin absorbed in the intestines, but it is known that achlorhydria is associated with an altered intestinal bacterial flora, which may interfere with the absorption of dietary vitamins

Treatment

Wernick's encephalopathy, or indeed any case of fulminating beriberi, is best treated by immediate administration of vitamin-B complex in large doses, at first intravenously and then intramuscularly and orally Admittedly aneurine alone can be successful (de Wardener and Lennox 1947), but deficiency of one vitamin alone is rare, and giving one vitamin in large doses to a patient with multiple deficiencies may precipitate acute deficiency states of the others (e g , Bichel and Meulengracht 1941) For instance, pellagra may be induced by giving aneurine or riboflavine to a malnourished person

Prognosis

The fate of 240 reported cases is summarised in the accompanying table 72% died Of those receiving parenteral aneurine, however little or late, 31% died, and of those who were not given aneurine 94% died Of the 68 survivors, 15 were described as being left with a residual Korsakow psychosis, 12 of them had had parenteral aneurine The chance of saving a patient's life depends on early and intensive treatment, and thus on early diagnosis If mental symptoms have already progressed to the confusional state before treatment has begun, memory may not be regained and delusions and confabulation may not cease for several months, or indeed ever

Summary

Fulminating beriberi developed in a woman resident in Great Britain

The disorder manifested itself as peripheral neuropathy and later (while the patient was in hospital) as acute Wernicke's encephalopathy, Korsakov psychosis, cardiac failure, and œdema The patient was later found to have advanced gastric atrophy

The disorder responded partially to vitamin therapy

We thank Dr C Foster Cooper for performing gastroscopy, and Dr F E E Sargent for the electromyography

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New Inventions

A NEW AIRWAY-GAG

FOR many years those who have administered electroconvulsion therapy with relaxants have utilised various forms of gags and airways, very often having to improvise because of the lack of reliability, in some cases, of the existing pieces of equipment In view of the various difficulties encountered, and the injuries caused to the teeth, tongue, lips, and throat of the patient, it is felt that this new combined airway-gag may fill a real need

The new airway-gag (see figures) is wedge-shaped, made exclusively of surgical rubber of average consistence, and comprises a thumb-grip, a body through which pass four channels, a flange extending round the thumb-grip and the body, a tongue depressor and retractor Of the four channels, through which oxygen or other gases may be administered, two are larger than the others and can be used for passing a stomach-tube (up to and including size 14) in unconscious states without dislodging the airway-gag—e g , in insulin-coma therapy, barbiturate poisoning, and recovery states

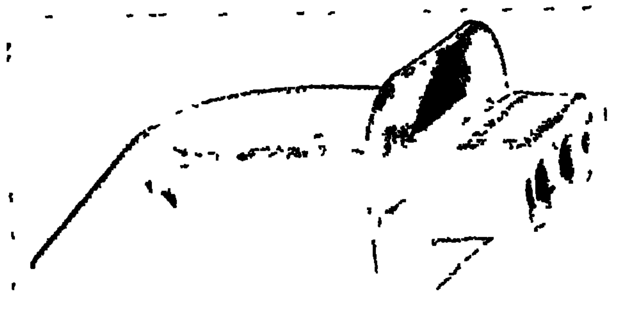
ADVANTAGES

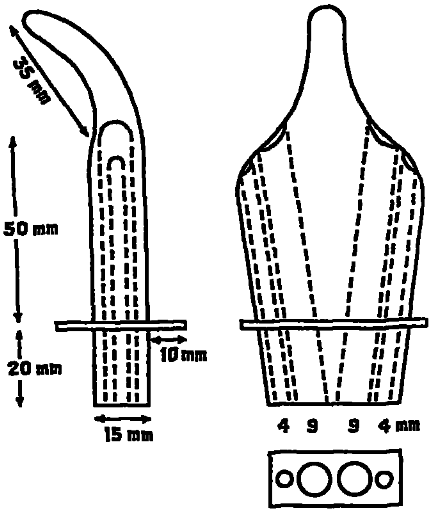
The airway-gag provides retraction of the tongue and reduces stertorous and noisy breathing It also accelerates pulmonary ventilation and oxygenation

During an electrically induced convulsion in which muscle relaxaans are used the patient can easily and adequately be protected from biting his tongue and/or lips and getting anoxæmia with increasing exhaustion

The tongue retractor holds the tongue on the floor of the mouth at all times, thus preventing one of the commonest causes of obstruction of the patient's airway—i e , allowing the tongue to fall back

The airway-gag cannot " wobble " in the mouth or occlude its air channels, thus stabilising the patient's respiration





The tongue retractor and depressor, because of its length, width and thickness, does not touch the pharyngeal wall, and thus trauma to the throat is prevented, and complaints of sore throats (sometimes experienced with airways) are eliminated The oxygen channels in the airway-gag are relatively short and can thus be easily examined for foreign bodies or unhygienic conditions

The airway-gag is easily cleaned and sterilised, it can be used for patients with or without teeth, and it can be used independently, with any apparatus used in electroconvulsive therapy, and with the larger face-masks

METHOD OF USE WITH RELAXANTS

By gripping the airway-gag with the thumb and index finger of the right hand and holding the tongue retractor pointing downwards there is little difficulty in inserting the airway-gag in the mouth The tongue retractor can be used to pull the tongue into position on the floor of the mouth, where it will remain during the treatment The airway-gag is inserted in such a way that the flange is closely apposed to the lips Sometimes, when the patient has very large jaws and a large mouth, it may be necessary for the flange to be closely apposed to the teeth

When the airway-gag is in position, the patient's lips are everted on the flange by sweeping one's fingers on the inner surface of the lips and drawing them outwards, this manœuvre prevents undue pressure on the lips and consequent soreness By applying a little glycerin on a piece of gauze to the lips, cracking of the mucosa (dried by atropine premedication) is eliminated or alleviated, and the lips are easier to evert—this also helps the airway-gag to slide into position more readily

The airway-gag has been used with both male and female adult patients having all shapes and sizes of jaws and mouths, with edentulous patients, and with those with deficient sets of teeth, but, because of the relatively even distribution of pressure all over the airway and the consistence of the rubber, little impairment of the surrounding structures has been experienced in the past year, during which the airway-gag has been in constant use

I wish to thank Sir Geoffrey Nightingale physician-superintendent of Warley Hospital Brentwood for help and advice The airway-gag is made by Messrs J G Franklin & Sons Ltd, 51, Manchester Street, Portman Square London, W 1

Warley Hospital
Brentwood Essex.

DESMOND C J O'CONNOR
L.R.C.P.I

A PORTABLE URINAL

THE purpose of the apparatus is to allow patients with urinary incontinence or nocturnal enuresis the comfort of a portable urinal that may be worn by day and by night It is suitable for ambulant or recumbent male or female patients

It consists of a thin waterproof bag worn under the perineum and between the thighs The bag is divided into two chambers, the first collects the urine (1, see figure) The second is larger and receives all the urine from the first chamber (2) For female patients the top of the bag is made concave to fit the vulva, for male patients the hole in the top is large enough for the genitalia to be inserted into the first compartment

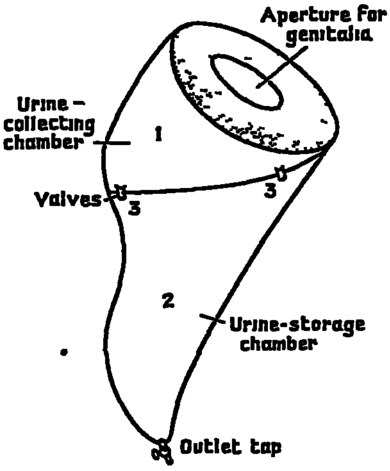


Fig 1

To prevent the urine from spilling backwards and overflowing, non-return valves (3) are situated between the chambers The valves are placed anteriorly and posteriorly in the wall separating these chambers This allows the patient to adopt any posture without inconvenience or risk of leakage

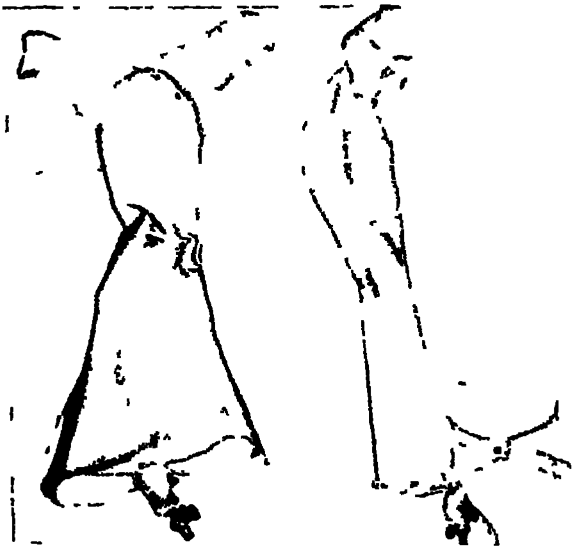


Fig 2.

After use, the appliance is emptied by a simple outlet tap at the lower end The whole apparatus is held in position by a halter of webbing around the waist (fig 2)

Messrs John Bell and Croyden (Surgical Appliance Department, 50, Wigmore-street, W 1) have manufactured this appliance in three sizes to my design, and it is obtainable from them It may be prescribed on National Health Service E C.10 forms

London, N 8

L. FRIDJOHN,
M A, M D Dubl, M R C.P I

Reviews of Books

Chronic Illness in the United States

Commission on Chronic Diseases Massachusetts Harvard University Press London Oxford University Press 1957
Pp 338 48s

THIS book is the first of four volumes to be published by the Commission on Chronic Illness, a voluntary body which studied chronic illness in the United States from 1949 to 1956 At the start, the reader may be awed by the countless people involved in this compilation thirty different societies helped, thirty various technical advisers advised, the commission itself had forty-six members Yet the book is excellent and presents a vast amount of assorted material in a readable, balanced, and well-set-out manner When there is little that can be done to prevent chronic illness the book says so When the cause of an illness is unknown or the accepted methods of treatment are valueless, no space is wasted on discussing improved theories or useless treatments, but the possible lines of fruitful research which might illuminate these dark areas of medicine are indicated

Yet when the factors causing a disease are understood and the prospects of preventing it are good, there is a clear authoritative survey of the position—for example, in tuberculosis, dental caries, retrolental fibroplasia, or rheumatic heart-disease Where there are futile preventive measures already in existence their futility is uncompromisingly exposed—e g , eighteen States forbid epileptics to marry and a federal statute forbids an epileptic to enter the country even for medical advice, and two States forbid a doctor to give advice on contraception

The work of reducing an almost boundless quantity of mental fodder to assimilable and appetising portions must have demanded exceptional editorial skill, especially since style and humour have remained intact The book is a valuable contribution to the growing subject of preventive medicine

The Strategy of the Genes

C H WADDINGTON, SC D , F R S , professor of animal genetics, University of Edinburgh London Allen & Unwin 1957
Pp 262 28s

THIS important book extends the theories of organic form in its widest sense, which Professor Waddington has developed elsewhere, to new fields—in particular to population genetics The form of the individual, reached in ontogeny, is the product of the action of natural selection upon natural populations in the past populations themselves have "forms", however, and the use of similar concepts in discussing the factors which determine and maintain organic pattern in the two cases, ontogenetic and phylogenetic, is more than an obvious analogy In Professor Waddington's hands it contributes some important ideas to evolutionary biology These are based on the picture of form and determination in both individuals and populations as equilibria, fixed or moving, derived from probability states on a contour-landscape, an idea which has already been used by Needham and others in describing embryogenesis

The author has devised a number of original and, in general, illuminating applications for this concept in evolutionary biology and epigenetics The chief merit of the book is its remarkable strictness in stating major hypotheses of the sort which have so often been made a subject for edifying or speculative philosophical treatment, in an experimentally investigable form, precise enough to be verified, at least in part, but wide enough in their implications to fill the gaps through which various kinds of vitalism intrude into biological thinking This is a major feat, and argument at this level calls for a very high order of exposition The book does not have the flair for making difficult ideas, of which it contains a number, immediately plain, but its quality makes the author fully entitled to expect some work from his readers Professor Waddington stakes a good deal of his success upon the fitness of the terminology he has devised to clarify his intentions Some new terms were essential Waddington's are not uniformly successful, though it would be a thankless task to better them "Creode", in particular, so spelled, suggests by derivation not "an appointed course of development" but "an object resembling meat", and "homeorrhesis" for homeostasis about a moving point is doubtfully necessary, but these are captious criticisms, and the terminology at least does not interfere with the argument

Waddington's most important discussion deals with the central paradox of orthodox evolutionary genetics—that on the one hand mutation is held to be predominantly random, and acquired characters not heritable, while on the other selection rapidly produces adaptation to a new environment, the necessary mutations appearing with remarkable aptness to enable the change to take place There is a definite gap between phenotypic adaptation, which is not inherited, and the heritable adaptations, exactly similar in their expression, which appear in subsequent generations Waddington's argument in partial resolution of this opposition—one of the "bifurcations of nature" to which Whitehead objected, and which looks inherently improbable—is too detailed to be fairly summarised, but it arises from his own research, and will stimulate experiment for many years to come in many laboratories The strict experimental orientation of his argument is impressive

The book is not one to be lightly attempted by general readers, but non-biologists who are willing to take trouble with it will find philosophy restored to its proper context in the laboratory The book concludes with a more strictly mathematical treatment, by Dr H Kacser, of the cybernetic systems involved in Waddington's arguments

The Clinical Examination of Patients with Organic Cerebral Disease

R KLEIN M D , consultant psychiatrist, Crichton Royal, Dumfries, W MAYER-GROSS, M D , F R C.P , senior fellow, department of experimental psychiatry, University of Birmingham London Cassell 1957 Pp 96 15s

THIS book is less ambitious in its scope than its title suggests, for the authors are concerned with disturbances of the more highly organised forms of behaviour rather than with the more obvious physical defects, such as hemiparesis and visual-field defect, which are so commonly seen in organic cerebral disease They do, however, give a concise description of the tests by which aphasia, agraphia, alexia, amusia, agnosia, dyspraxia, acalculia, autotopagnosia, and similar disorders can be detected and investigated They discuss these phenomena sufficiently to explain the tests

Many doctors who find these disorders hard to understand, and harder to identify in the individual patient, will be glad to have this information, otherwise available only in scattered articles, brought together in one small book The presentation is as simple as the complexity of the subject permits

Manual of Stomatology for Dental and Medical Practitioners

J P WALSH, M B , D D SC , F D.S R C.S , professor of dentistry, dean and director, University of Otago Dental School New Zealand
N M Peryer London Lloyd-Luke 1957 Pp 130 30s

THIS small book covers all that a medical student needs to know on the purely dental aspects of the mouth There is also a general survey of the oral manifestations of systemic disease which will serve as a reminder to doctors but is not sufficiently descriptive to be much help to the dental surgeon The line drawings are good and the photographs excellent—and their quality may be reflected in the price of the book

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Drug Resistance in Micro-organisms (Ciba Foundation Symposium London J & A Churchill 1957 Pp 352 50s)—Concerned at the lack of basic knowledge and the empiricism of the clinical approach to chemotherapy, Sir Charles Harington suggested a symposium to the director of the Ciba Foundation He took the chair at a conference held last March, and the papers are here edited by Dr G E W Wolstenholme and Miss C. M O Connor

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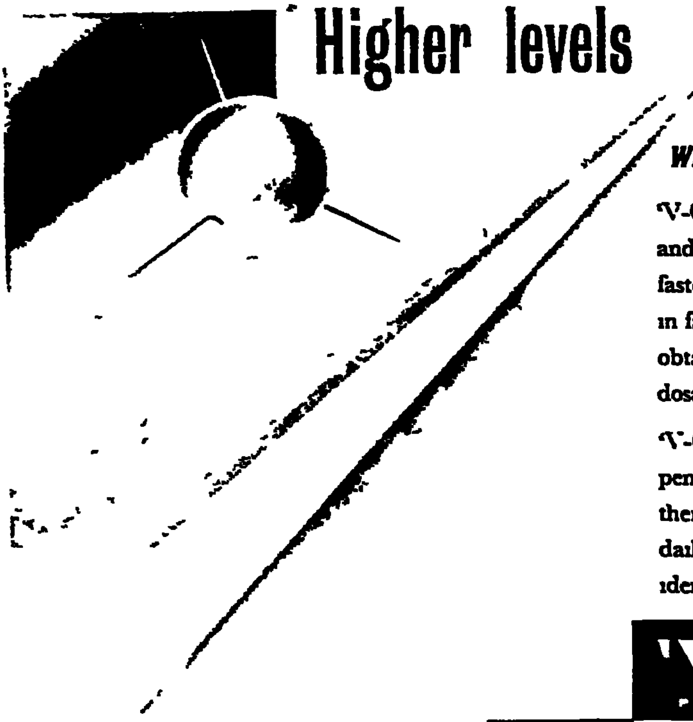

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THE LANCET

LONDON 15 FEBRUARY 1958

Leucocyte Agglutinins and Blood-transfusions

AGGLUTININS that affect red blood-cells are familiar to all, agglutinins that involve blood-platelets have been known and studied for some time, but agglutinins that cause aggregation and possibly destruction of leucocytes have been studied for only a few years, and the idea that leucocyte agglutinins may be responsible for transfusion reactions has appeared quite recently. Leucocyte agglutinins were first identified by MOESCHLIN and WAGNER,[1] in 1952, in the blood of a patient who had agranulocytosis caused by amidopyrine, later in the same year a similar report was published by DAUSSET and NENNA.[2] DAUSSET and his colleagues at the Centre National de Transfusion Sanguine in Paris have carried out considerable research into the detection, properties, and incidence of leucoagglutinins.[3]

All who have worked on leucoagglutinins emphasise the importance of adopting a technique that gives reproducible results and can be properly controlled. Leucocytes for use in the tests are obtained by sedimentation from defibrinated blood after the addition of polyvinyl pyrrolidone or dextran, blood compatible with the serum to be tested must be used to avoid false results due to agglutination of red cells. The test serum is first heated for 10–30 minutes at 56°C, the leucocyte suspension is added and the mixture put in an incubator at 37°C for an hour. It has been found that for easy reading a leucocyte suspension of 5000 to 10,000 per c mm should be used. The mixture is examined with a low-power microscope, and the result reported as negative or in various grades of positive. DAUSSET et al [3] discuss the pros and cons of various alternative techniques and point out that the use of siliconed glassware will give false negative results.

The leucocyte agglutinins so far found are all isoagglutinins—i e, they do not react with the leucocytes of the patient himself but only with other persons' normal leucocytes, autoleucoagglutinins have not been convincingly demonstrated, and DAUSSET[4] failed to find evidence of autoactivity in the sera of 26 patients who had leucoagglutinins present. Examination of the properties of these leucocyte agglutinins shows that they are relatively thermostable, they can be preserved by freezing, and they are probably, like other antibodies, gamma-globulins. They are most active at 37°C, and their activity can be demonstrated in saline as well as serum media over a wide range of pH from 6 5 to 9 2. They will agglutinate normal and pathological granulocytes and lymphocytes, and can be shown to be absorbed from serum by leucocyte suspensions, their action on primitive leucocytes is uncertain. DAUSSET et al have shown that serum contains a thermolabile factor which inhibits leucoagglutinins, and this is destroyed by heating to 56°C for up to 30 minutes. The immune nature of the leucoagglutinins, already suggested by their gamma-globulin character and their absorption by normal leucocytes, was further confirmed by their passive transfer. DAUSSET et al injected serum with leucoagglutinin activity into two recipients, in each case there was a rapid and profound fall of the recipient's white-cell count, whereas injection of normal serum had no effect. Some workers have concluded that human leucocytes possess A and B antigens like those found in erythrocytes, RIIS,[5] for instance, reported that human leucocytes clumped together in anti-A or anti-B sera in accordance with the ABO groups of the leucocyte donors. But doubt has been thrown on the validity of this sort of result by the more recent studies of BAKEMEIER and SWISHER,[6] who have shown that erythrocyte "ghosts" can be demonstrated in the leucocyte clumps and may well be responsible for these observations.

In addition to the very few cases of drug-induced agranulocytosis, leucoagglutinins appear to be present in the serum of a miscellaneous group of patients. DAUSSET et al examined more than 2000 sera, 500 were of patients with various diseases, of whom 102 had leucopenia, of these 102, leucoagglutinins were detected in only 19. These 19 patients comprised 1 case of amidopyrine agranulocytosis, 3 of paroxysmal nocturnal hæmoglobinuria, 2 of acute leukæmia, 1 of Hodgkin's disease and 2 of lymphosarcoma, 1 of Felty's syndrome, 1 of anæmia secondary to congenital angiomatosis, and 8 of chronic refractory anæmia and leucopenia. Other results have suggested that leucoagglutinins are not limited to patients with leucopenia, thus PAYNE[7] examined the sera of 350 patients with various hæmatological diseases and found leucoagglutinins in 38, 26 of these patients had neither neutropenia nor leucopenia. DAUSSET[4] pointed out, however, that nearly all patients with leucoagglutinins in the serum had received multiple blood-transfusions, and of 60 patients with leucoagglutinins, 90% had been transfused several times. Among the 19 patients of DAUSSET et al, all except the patient with amidopyrine agranulocytosis had received transfusions. PAYNE's series of patients with blood diseases included 49 who had had more than ten transfusions, 19 had leucoagglutinins present, 30 had not, she points out that the fact that blood-transfusion is the common factor in so many cases fits in with the finding that leucoagglutinins are isoantibodies and so do not act on the patient's own leucocytes. "From the standpoint of the recipient," says PAYNE, "the presence of an isoleukoagglutinin in his own serum offers an additional factor to be considered in transfusion reactions."

The hypothesis that unexplained transfusion reactions may be due to the presence of agglutinins affecting leucocytes has been explored by BRITTINGHAM and CHAPLIN,[8] who at the same time looked for platelet

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gglutinins Transfusion reactions that cannot be
ttributed to unexpected red-cell agglutinins are par-
icularly liable to be troublesome in patients receiving
ultiple transfusions—say for the treatment of aplastic
næmia BRITTINGHAM and CHAPLIN selected 5 patients,
nown to be prone to febrile transfusion reactions, who
ad received 20–85 transfusions, for a control series
hey had 5 other patients who had received 2–7 trans-
usions and had had no recorded reactions The blood
o be given to these two groups was separated by differ-
ntial centrifuging into two fractions a leucocyte-rich
raction which contained nearly all the leucocytes and
early all the platelets as well, and a leucocyte-free frac-
ion which was also almost free of platelets, the two
ractions were transfused on separate occasions The
eucocyte-rich fraction caused febrile transfusion reac-
ions in all 5 test patients, and leucoagglutinins against
he donor cells were found in the sera of all of them,
arying in titre from 1 in 4 to 1 in 512 The leucocyte-
ree fraction caused no reactions in the test patients
Neither the leucocyte-rich nor the leucocyte-free frac-
ions caused any reaction in the 5 control patients
Platelet agglutinins did not seem to be important,
hey appeared in any strength in the serum of only 1
est patient

These findings confirm that leucoagglutinins may
vell be the cause of hitherto unexplained transfusion
eactions, and it is clear that laboratories supervising
he preparation of blood suitable for patients known to
e liable to these reactions should include examination
f the recipient's serum for leucoagglutinins among the
ests to be carried out Anyone proposing to undertake
hese tests could study with advantage an account by
WALFORD et al,[9] who describe suitable techniques in
etail They consider that the test is reliable provided
he following points are adhered to a strongly positive
ontrol (e g, a high-titre immune rabbit serum) and at
east two negative serum controls should be included in
ach set of tests, a positive test should show definite
lumps of agglutinated leucocytes *and* very few leuco-
ytes between the clumps, and the positive result
hould be consistently reproducible

If reactions develop in a patient receiving multiple
ransfusions, and a leucoagglutinin is found in his
erum, then the problem of how to give blood free, or
lmost free, from leucocytes has to be considered A
ifferential centrifuge method such as that of BRITTING-
HAM and CHAPLIN can be used, but this involves a
efrigerated centrifuge, and they had the advantage of
sing blood collected in plastic bags CHAPLIN is testing
n alternative method which does not involve centri-
ugation, in this method the red blood-cells are sedi-
mented in dextran, and effective removal of 95% of the
uffy coat with retention of 98% of the donor red cells
or transfusion is claimed We hope that this method
ill pass its clinical trials, because these patients,
hough relatively few, present an increasing problem
ow that long-term programmes of repeated blood-
ransfusion can be undertaken by so many hospitals

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[9] Walford R L, Peterson E T, Doyle P *Blood*, 1957, 12, 953

Mitral Stenosis and Mitral Incompetence

THE distinction between mitral-valve obstruction and regurgitation has assumed great practical importance Rheumatic endocarditis involving the mitral valve may produce pure stenosis, free regurgitation, or obstruction combined with incompetence There is a wide spectrum between the extremes of pure severe stenosis and gross incompetence unaccompanied by narrowing of the valve orifice Usually pure stenosis gives rise to an easily recognised clinical picture, and can be readily distinguished from pure incompetence [1] Difficulty in exact diagnosis arises when stenosis and incompetence coexist Mitral valvotomy, which gives striking relief in pure stenosis, may be valueless or even harmful when incompetence is severe Differentiation is therefore important, in WOOD's [2] series of 300 unselected cases of mitral-valve disease mitral incompetence was the dominant hæmodynamic lesion in 34%, in half of these stenosis was also present but was dominated by incompetence

Much study has been directed to the accurate assessment of stenosis and incompetence, and McDONALD and his colleagues [3] have lately reported an intensive clinical and hæmodynamic study of 44 patients with severe symptoms due to mitral disease who required surgical relief The mitral regurgitant flow was calculated from preoperative cardiac-catheterisation data, and from the estimated valve size at operation [4] The valve size and regurgitant flow were compared with the clinical, radiographic, and electrocardiographic signs

The clinical history did not differentiate between dominant stenosis and incompetence Fatigue, in addition to dyspnœa, was found in all types of case and was thought to be due to a low cardiac output Hæmoptysis was rather less common in dominant incompetence than in dominant stenosis, and a history of systemic embolism was not obtained from patients with the largest valves On examination, the signs of severe incompetence tallied well with the usually accepted criteria a localised thrusting cardiac impulse denoting left ventricular hypertrophy, a normal or soft first heart-sound at the apex, a third heart-sound, and a pansystolic apical murmur conducted to the axilla The arterial pulse was of smaller volume in patients with pure severe stenosis than in those with dominant incompetence There were, however, exceptions A third heart-sound was detected in 4 patients with severe stenosis, instead of the usual opening snap Damping of the first sound and opening snap is sometimes referable to calcification of the valve [5] McDONALD et al emphasise the importance of the opening snap in the diagnosis of stenosis [6], a loud snap suggests a pliable valve amenable to surgery They do not comment on the timing of the snap, which is now generally held to be of value in determining the degree of stenosis the earlier the snap after the second heart-sound, the tighter the stenosis[7] The typical mitral diastolic murmur was present in all patients save one, but its intensity was not related to valve size. The length of the murmur was thought to be proportional to the severity of the stenosis Apical systolic murmurs were louder in patients with significant incompetence than in those without, but soft systolic murmurs were heard in patients with pure stenosis, if atrial fibrillation was present When gross incompetence was present a loud systolic murmur was heard, and absence of such a murmur virtually excluded incompetence In intermediate cases the intensity of the systolic murmur did not indicate the degree of incompetence It is important to distinguish the pansystolic murmur of mitral incompetence from that of tricuspid incompetence, and from the ejection murmur of aortic stenosis

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[1] Brigden W Leatham A *Brit Heart J* 1953, 15 55
[2] Wood P *Brit med J* 1954 i 1051 1113
[3] McDonald L Dealy J B, Rabinowitz M Dexter L *Medicine Baltimore* 1957, 36 237
[4] Gorlin R Dexter L *Amer Heart J* 1952 43 188
[5] Wynn A *Brit Heart J* 1953, 15 214
[6] Mounsey, J P D *Ibid* p 135

Radiographic studies confirmed the clinical findings of enlargement of the right ventricle in pure stenosis, and of the left in pure incompetence Enlargement of the right ventricle was greatest in patients with the smallest valves Left ventricular enlargement usually indicated significant incompetence but was present in 4 cases with pure stenosis, in the absence of any other cause The right ventricle was enlarged in mitral incompetence when the pulmonary resistance was raised, and McDONALD et al point out that such enlargement does not exclude the presence of severe incompetence The size of the left atrium was not helpful in assessing valve size, severe incompetence was usually accompanied by a large left atrium, but this was occasionally seen with pure stenosis, as others have found.[8 9] Systolic expansion of the left atrium was of no value in distinguishing incompetence from stenosis Calcification of the mitral valve was common but was not specially associated with incompetence—a finding which differs from that of WYNN[5] Little differential diagnostic help was apparently gained from radiographic signs of pulmonary venous and arterial hypertension[10 11], perhaps this is so because the lung changes correlate best with increases in pulmonary vascular resistance, which can be present in both incompetence and stenosis

The electrocardiogram showed evidence of right ventricular hypertrophy in pure severe stenosis when the pulmonary vascular resistance was appreciably raised, but of left ventricular hypertrophy in severe incompetence. In intermediate cases there was evidence of biventricular hypertrophy or normal ventricular balance Broad and notched " mitral " P waves due to left atrial enlargement did not differentiate between incompetence and stenosis, but atrial fibrillation was universal in the cases of frank incompetence, whereas many with pure stenosis had sinus rhythm Hæmodynamic studies showed that when mitral disease was severe the dominant lesion (stenosis or incompetence) was closely related to forward mitral-valve area Significant incompetence was exceptional with the smallest valves, while dominant incompetence was the rule with the larger valves Between the extremes was a wide spectrum in which dominant stenosis shaded gradually into dominant incompetence Pulmonary vascular resistance was highest in patients with pure stenosis, but considerable increases in resistance were also found in incompetence Like other workers,[12] McDONALD et al obtained little diagnostic help from the form of the pulmonary capillary venous pulse, a large v wave often being found in both stenosis and incompetence They hold that more information is needed about the estimation of the rate of descent of the y wave, expressed as the " Ry/v ratio " of OWEN and WOOD[13] But a slow " y " descent is helpful in suggesting mitral obstruction

This valuable contribution lends weight to the accepted criteria for the diagnosis of mitral incompetence, and suggests that combined clinical, radiographic, and electrocardiographic examination usually provides the best estimate of the relative contributions of stenosis and incompetence But difficulty exists in many cases, and the refinements in diagnostic method still needed may be provided by the dye-dilution techniques of KORNER and SHILLINGFORD[14] Other techniques, involving puncture of the left atrium[15-17] and consecutive measurements of left atrial and ventricular pressures, may yield useful information, but simultaneous measurement of flow is necessary for diagnostic certainty

Epilepsy and Hysteria

FASHIONS in disease are imposed not only by medical opinion but also by the *Zeitgeist* Few doctors now see *la grande crise d'hystérie*—the major hysterical fit which used to be an important and sometimes difficult differential diagnosis from epilepsy CHARCOT,[18] in the dawn of modern clinical neurology, made the distinction with his usual clinical shrewdness, and the main differences that he noted continue to guide us There were cases, however, in which he found it hard on semeiological (and, one suspects, on ætiological) grounds to separate the two These he referred to as " hystero-epilepsy ". The term and the concept were not generally accepted by a later generation of French neurologists BABINSKI,[19] for instance, insisted that all cases could be put into one or other category BUMKE[20] in Germany was equally emphatic ALDREN TURNER[21] in this country was less dogmatic but in general hystero-epilepsy was regarded with suspicion The ætiological segregation of the two conditions—and this was the real point at issue—was considered to be complete The problem was shelved rather than solved, and KRAPF[22] has lately reviewed it

Diagnosis has always been difficult in the cases with

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7 Wells B *Brit Heart J* 1954 16 261
8 Venner A *Brit med J* 1954 i 1359
9 Goodwin J F Hunter J D Cleland, W P, Davies L G Steiner R E *Brit med J* 1955 ii 573
10 Davies, L G Goodwin, J F Steiner R. E. Van Leuven B D *Brit Heart J* 1953 15 393
11 Short D S *Brit Heart J* 1955 17 33
12. Wynn A., Matthews M B, McMillan K R., Daley, R. *Lancet*, 1952, ii, 216
13 Owen, S G, Wood P *Brit Heart J* 1955, 17, 41
14 Korner P L, Shillingford, J P *Clin Sci* 1955, 14, 553
15 Radner S *Acta med scand* 1955, 152, 1
16 Morrow, A G, Braunwald E. Haller, J A, Sharp, E H *Circulation*, 1957 16 399
17 Björk V O *Acta chir scand* 1954, 107 466
18 Charcot J M Lectures on Diseases of the Nervous System. London, 1877
19 Babinski J Ma conception de l'hystérie. Chartres 1906
20 Bumke O Handbuch der inneren Medizin. Berlin 1926
21 Turner W A Epilepsy London 1907
22. Krapf E. E. *Bull World Hlth Org* 1957, 16 749

features of both epilepsy and hysteria, and it was usual to suggest that hysteria happened to coincide with epilepsy, just as it might with any other organic condition In some cases the concept of "affective epilepsy"—a form of reflex epilepsy in which the afferent stimulus was an emotional one—was a help, but many could not be forced into this mould With the advent of the electroencephalogram (E E G) the differentiation should *have become easier, for if epilepsy is a specific cerebral* dysrhythmia this can surely be recognised on the E E G , and if the dysrhythmia is not present the attacks cannot be epileptic Unfortunately, with growing knowledge of the E E G , this argument is not as convincing as it was E E G records are still useful diagnostically, but it has become clear that some abnormalities are not a specific epileptic dysrhythmia but are somewhat similar to such dysrhythmia, and commonly these are found in just those patients whose abnormal behaviour raises the possibility of a psychiatric diagnosis Thus aggressive psychopaths, and indeed inadequate psychopaths too, in whom hysterical features are readily found, have abnormal E E G s which represent in part a defect of "maturation" of the electrical record In aggregate these can probably be distinguished from a group of epileptic records, but distinction in individual cases may be very hard

Growing recognition and exploration of the temporal-lobe group of epilepsies further obscures the borderline (CHARCOT's own description of hystero-epilepsy reads very like an example of temporal-lobe epilepsy) Here undoubted *epilepsy* occurs in a setting of behaviour disorder and emotional abnormality, and individual fits sometimes appear to have a mental cause Indeed, for epilepsy in general BARKER[23] and others have made the wider claim that with abreactive and suggestion techniques an appropriate psychological stimulus will reproduce specific epileptic activity, both electroencephalographic and clinical Conversely formal psychotherapy, particularly where specific psychogenic features can be uncovered, may very occasionally have a dramatic effect on epilepsy, and the psychotherapy of environmental adjustment may be more often effective though less dramatic

It seems that we must reconsider the concept of hystero-epilepsy, not in the form that CHARCOT put it forward, but as a more fundamental problem in the physical and mental genesis of epilepsy The clinical problem may be small, but the idea behind it is important In these days of psychosomatic medicine it is as well to try and see the reality behind the phrase

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[23] Barker, W *Res Publ Ass nerv ment Dis* 1950, 29, 90

Annotations

TRUANTS IN INDUSTRY

Shepherd and Walker[1] have studied the relation of absence from work and overtime working, on the one hand, to wage level and the number of dependants on the other Their investigation was made in 1952 in a large iron and steel works where wage differences depend on promotion grades and do not sharply reflect differences in skill or responsibility, and bonuses bear little relation to individual productivity The difference in gross annual wages between the highest and lowest paid groups was £300 The data were taken from absence records, nearly equal numbers of men were selected in each of six wage-groups, matched for average age, income-tax code-number (as an index of the number of dependants), heaviness of work, and temperature of working conditions The number of absences and total duration of absence (as number of shifts lost) were calculated per 100 men in each group, and divided into absence due to sickness, due to injury, with permission, and without permission

Certain trends were obvious The absence-rate was high in the lowest-paid group, mainly through more absences without permission and more long absences with permission In other groups the number of absences and of shifts lost increased with increasing wages Absence without permission increased with increasing wages, but this did not hold for the highest and lowest wage-groups At higher wage levels the high total number of absences was caused by absences without permission, but the large number of shifts lost was caused mainly by more recorded sickness There was no evident a-priori reason to expect a greater incidence of sickness in the higher-paid group (indeed, in an outbreak of influenza the previous year the incidence had been much higher in the lower-paid workers) Shepherd and Walker believe that the difference was caused by a greater tendency to go absent (for illness or other reason) and a tendency to stay away longer for a given illness in the higher-wage group, and by differences in reporting illness At lower wage levels many absences of medium length were probably due to sickness, though not reported as such Thus there were many more absences (recorded as "without permission", not as "due to sickness") of four to nine shifts' duration than of two or three shifts' duration, this would accord with their being caused by sickness, because of the National Insurance sickness-benefit regulations

Absence-rates also varied according to family responsibility they were high for single men, lowest for those with two dependants, and higher again for those with more, this was true for both the higher-paid and the lower-paid workers The amount of overtime worked increased with number of dependants in the case of the lower-paid workers, but there was no such relationship among the higher-paid workers—perhaps partly because of income-tax differentials The lowest-paid group had the highest overtime figures as well as a high absence-rate

Shepherd and Walker differentiate between an individual "absence threshold", determined by long-term factors, both personal and general, and the immediate factors which raise the question of whether or not to go absent and may be powerful enough to exceed the threshold One step towards "coping with absence", they say, lies in discovering the associations between absence and such factors as number of dependants, time of day (e g , single-shift absences without permission have been shown to be commonest in the morning shift[2]), or day of the week Their investigation indicates that wage-level is an important factor

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[1] Shepherd R D , Walker, J *Brit J industr Med* 1958, 15, 52

[2] Shepherd, R D , Walker, J *occup Psychol* 1956, 30 105

Discussion of absence from industry nearly always starts from the point of view of employers, whether private or public, or of society as a whole , and strong pressure may be put on individual workers to stay at their jobs unless circumstances are exceptional Dr D H Stott[3] finds that this pressure is likely to increase

> "We have to recognise that the static, self-indulgent pattern of living is out of place in the modern world If one of a gang of roadworkers stayed at home to tend his pigeons the loss would be just that of his day's labour But now excavating is done by mechanical monsters, if the trained man working one takes a day off the whole job is held up"

At present, absence from work is especially common, and especially deprecated, in coalmining—which, as has been lately pointed out,[4] is one of the few remaining industries where a man can earn enough to afford an occasional unpaid day's leisure if the fancy takes him, and which therefore attracts men to whom this freedom appeals The anxiety felt about absence from work stems largely from society's overwhelming need to increase production in a competitive or warring world But from the individual's point of view, it will be a poor world if we became rich in the goods produced by industry at the expense of being tied rigidly to our work That, rather than conquest by "universal robots", might be the way in which machines could come to dominate us—not only the mechanical devices for production but the mechanical organisation of society

REFLEX ANURIA

SUPPRESSION of renal function occasionally follows instrumental procedures on the renal tract, or the sudden relief of chronic urinary retention, it may arise in an apparently healthy kidney when the contralateral organ becomes acutely obstructed, as by a calculus, and rarely it follows certain gynæcological and obstetric operations in which the urinary tract has not apparently been primarily involved To this condition, with such diverse causes, the name "reflex anuria" has been given, and it has generally been assumed to be caused by excessive stimulation of the sympathetic nervous system, which induces either reflex renal ischæmia or overproduction of pituitary antidiuretic hormone The possibility that some cases may be due to postrenal obstructive causes has tended to become overlooked, and, since the oliguria is often transient, the need to inquire further seldom arises

Sirota and Narins[5] report three cases in which an obstructive lesion was evident, in the form of gross bullous œdema at the ureteric orifices In two of these cases both ureters had previously been catheterised in the normal way, in the third case nephrectomy had been carried out shortly after catheterisation of the opposite side In all three cases severe oliguria and progressive azotæmia and hypertension had followed the ureteric manipulation. A second cystoscopy confirmed the presence of obstruction due to œdema at the orifices, with absence of normal effluxes, and in each case the condition was relieved by the reinsertion of indwelling ureteric catheters Since there was no apparent technical difficulty at the time of the initial investigation, Sirota and Narins conclude that the œdema may have been induced by an idiosyncratic response to trauma, to the formaldehyde used for catheter sterilisation, or to the contrast medium used for retrograde pyelography

Such sensitivity can be assumed to be rare, but these cases are a reminder of the need for preliminary inquiry and for careful washing of all the instruments before making this commonplace examination

SALARIES OF HOSPITAL EMPLOYEES

THE National and Local Government Officers Association (NALGO)[1] have surveyed the salaries and work of more than a quarter of all administrative and clerical workers in the National Health Service to find that 36% earn less than £400 a year, 46% earn £400–£600, 10% earn £600–£800, 5% earn £800–£1200, and 3% over £1200 More than 80% are thus earning less than the weekly *£12 1s 6d* earned by a *male manual* worker The modest rises which these workers have received over the past ten years have not been enough to keep pace with inflation Thus though a man who was earning £385 in 1948 is now earning *£515* the cash value of his earnings would have been only about £325 in 1948 Compared with his colleagues on the same salary in other services he has had a poor deal His effective salary has fallen by 15% compared with 1% in the Civil Service

The Guillebaud and the Hall Committees, both valuable outside opinions, have confirmed the inside opinion of hospital administrators that the present rates of pay are threatening efficiency and injuring recruitment, yet NALGO's survey shows that few offices are "seriously below establishment" This may perhaps mask some of the dangers of the situation The posts are apparently only being filled after repeated, and expensive, advertisements Too many of the staff are drawn from elderly retired men and married women. These workers are often skilled and conscientious and their help is valued, but they are not "promotion material" The few young people who join the service do not stay and are often unsuitable Older men and women who find the work satisfying and who have pension rights are understandably less likely to leave, though even in this group there have been some reluctant defaulters At present they are overworked and spend too much of their time training the constantly changing junior staff, and checking and supervising their work. NALGO's survey gives as examples of this overbrisk turnover a south-eastern hospital group that has replaced a third of its staff in two years, a London group that has replaced two-thirds in the same period, and a west country group that has replaced the whole of its finance department since January, 1955

The present economy in salaries seems to be causing not only inefficiency but also extravagance. Advertising over the whole country must, it is estimated, cost about £500,000 a year Agency typists are often employed as stop-gaps and earn more money and work shorter hours than the permanent staff

The recommendations of the Hall report,[2] which are at present being considered by a joint sub-committee of the Whitley Council, would do much to right the situation It is important that the hospital service should be able to attract and retain its fair share of competent young men and women who will be willing and able to take advantage of the opportunities for training and promotion which it should offer But we live in a century, to look no further, in which there are likely to be more and more old people and fewer young people The health service would be sensible to remember the help that pensioners and married women have given in these difficult times Even in easier times they could offer valuable support to the recruits whom we all hope the service will get, and for themselves have the healthy satisfaction of doing a worth-while job

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[3] Stott, D H Present Needs in Our Work Among Youth London, 1958 See *Lancet* Feb 8, 1958, p 305

[4] See *Observer*, Jan 5 1958

[5] Sirota, J H, Narins, L *New Engl J Med* 1957, 257, 1111

[1] *Publ Serv* February, 1958, p 38

[2] See *Lancet*, 1957, i, 1104

THE SECOND STAGE

In these days of strict training for natural childbirth it is widely held that the first stage of labour should normally be a time of rest and relaxation in an atmosphere of quiet efficiency The time for hard physical effort comes later, in the second stage A first labour is seldom concluded naturally without at least a short period of pushing by the mother to assist the uterine action But it is perhaps not always remembered that much of the second stage needs no help from the mother, the uterus alone advancing the presenting part down to the perineum A patient who is urged to push too early in the second stage may achieve little which could not be done as well by the unaided uterus, her exertions leaving her exhausted towards the end of her labour when her efforts are required Constance Beynon[1] believes that there are other disadvantages both to too early and to too vigorous pushing She points out that the secondary powers applied while the presenting part is still gripped by the cervix or the upper vagina—broadly the site of insertion of the transverse cervical ligaments—will produce on these important supporting structures a downward thrust which may well be a significant factor in the causation of vault prolapse Similarly, straining efforts made while part of the anterior vaginal wall is below the head may result in this part of the wall being rolled down beneath the head with potential damage to the underlying structures around the bladder base, perhaps leading to stress incontinence Mrs Beynon believes that these tendencies will be slighter in the absence of straining efforts, since the early part of each contraction pulls the vagina taut and prevents it and the structures deep to it being pushed down in front of the presenting part She likens the process to a sleeve with a loose lining the slower the arm is passed down the sleeve the less the tendency for the lining to roll out at the wrist, especially if the lining is held firmly at the top

Theoretical considerations apart, Mrs Beynon's method of allowing the patients to follow their own inclinations in the second stage of labour, forbidding any mention of pushing by those in attendance, seems to prove its worth in practice In a clinical trial a much shorter period of pushing and a lower forceps and perineal-laceration rates were found in patients managed in this way than in a second group more actively encouraged to push the child out Although, because of variable factors, this was not strictly a controlled trial, the method seems to have much to commend it Thus, the atmosphere of tranquillity which she describes in the second stage contrasts sharply with the scenes of violent muscular effort when the "labouring" woman is persistently urged to take an active part

For the normal case this policy of non-intervention seems reasonable There are circumstances, however, in which the vigorous cooperation of the patient can contribute significantly to the safe delivery of her child Breech delivery, for instance, achieved by the patient's efforts with minimal interference by the attendants is greatly to be preferred to breech extraction under general anæsthesia Rarely in the multipara the pains will almost disappear in the second stage, leaving the head stationary in the middle or lower part of the pelvis, and here, as with the breech which the patient cannot quite push over the perineum, brief adoption of the squatting position may have dramatic effects

ARMY MEDICAL HISTORY ON SHOW

It seems that in this country few museums, apart from the famous national ones, can be said to prosper[1], and if many of the rest are ill attended it may be because they are ill tended But no such accusation can be laid against the R A M C Historical Museum, at Crookham Built up in the past five years by Major-General R E Barnsley, who remains the curator, this collection sparkles, and its existence should be more widely known

The collection is mainly for the non-specialist the muniments section is held elsewhere (at the R A M College, Millbank), and no effort has been made to duplicate the purely technical collections that were already in being But, without entering into technicalities, this group of apparatus, models, plaques, letters, drawings, photographs, standards, medals, and so on illustrates brilliantly the development of the Army medical services from the time of the Peninsular War, in which the Duke of Wellington had miserably small medical resources at his command, down to and beyond the war of 1939–45, with Field-Marshal Montgomery writing soon after its termination of a Corps "whose contribution to victory has been beyond all calculation"

The medical relics include "Dr Wilde's electric alarum indicator with insulated explorer and forceps," which puts far back into the 19th century the date when metallic foreign bodies—in this case bullets—were first localised electrically[2] There is a wealth of paramedical objects—including a letter from the indefatigable Miss Nightingale, who took time off at Scutari to communicate at some length with a young admirer in England Also on view is a quilt knitted by Queen Victoria for patients at Netley Hospital (There is an old story, probably apocryphal, that this was applied only to fortify the dying, but, as this became widely known, its single purpose may not have been wholly achieved) Inevitably, too, the museum shows something of our military history proper (Who knows the origin of "Thomas Atkins"?) And for the unwarlike it provides welcome evidence of evolution from the days, not so long ago, of the cat-o'-nine-tails, of branding deserters, and of "crime-and-punishment" books whose every page is filled with charges of drunkenness

The collection reveals doctors, in war and in peace, as incorrigible magpies the trophies range from a Russian drum won at Sebastopol to a Coptic cross collected by a surgeon in Lord Napier's Abyssinian Campaign of 1868 Perhaps the keenest medical collector of all is General Barnsley himself, who (ignoring the adage that good wine needs no bush) is at present bent on discovering a pre-1914 horse-drawn heavy ambulance-wagon to place outside the museum—perhaps hoping thus to distinguish it, for the benefit of visitors, from the commandant's office nearby Any reader lighting on a disused horse-drawn heavy ambulance-wagon in his garage is invited to offer it to the museum

The museum is open to the public on Mondays to Fridays from 10 A.M till noon and from 5 till 7 P M, and on Saturdays from 10 A M till noon Visitors are welcome at other times, including Sundays, but are asked to write in advance to the Curator, R A M C Historical Museum, Queen Elizabeth Barracks, Crookham, Hants

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1 J Obstet Gynæc Brit Emp 1957 64 815

1 See Manchester Guardian Feb 5 and 6 1959

2 See Sutton C Lancet, 1957, ii, 1174

Special Articles

INCIDENCE OF WOUND INFECTION

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M A, M D Edin, F R C S E
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For some time the surgeons at the Edinburgh Royal Infirmary have been concerned with the frequency with which their operation wounds become infected As in many other old-established hospitals, the operating-theatres of the Infirmary are under suspicion because of out-of-date sterilising equipment and inefficient ventilation systems Before major improvements were started, we thought it desirable to know the present incidence of wound infection which would serve as a basis for comparison in the future, and in addition we hoped that this survey would help us in formulating a satisfactory routine method of recording infection for our hospital

The true figures of wound infection in a busy hospital are more difficult to obtain than appears at first sight There is the possibility that the incidence will vary at different times of the year, month, or week This means that records should be kept over an entire year and in greater detail than is customary in the patient's case-record or in a " wound book " The practice of keeping a wound book is good, but to measure the incidence of wound infection from it can be misleading because the entries in the book and the abstraction of the information are usually done in retrospect and may not give a complete account of the infection Anything less than frank sepsis is apt to be omitted There are also administrative problems in ensuring that the wounds are followed up over a sufficiently long time and with sufficient care to know whether or not infection has in fact taken place This may be particularly difficult when surgical cases are transferred to convalescent homes, sometimes a few days after operation, with a consequent break in the continuity of observation and recording Finally, the criteria of infection and degree of infection have to be established and made uniform throughout the wards where the recording is being done

Procedure

The investigation was made in four surgical charges the neurosurgical charge, the orthopædic charge, and two general-surgery charges for three months from October to December, 1956 Every case passing through the operating-theatres of these charges was followed up meticulously, and the wound, whether incisional by operation or accidental, was assessed as regards cleanliness and infection while healing It was decided to make the assessment of infection entirely clinical, but provision was made whereby particulars of bacteriology and chemotherapy could be correlated later

Precoded forms were printed and kept in the operating-theatre precincts, and on completion of the operation the surgeon or one of his assistants filled in the main particulars—e g , name and age of patient, type of operation, and nature of the wound While the patient remained in hospital the forms were kept with the patient's case-notes

The method of current recording of the state of the wounds varied a little from ward to ward, but in all wards, whenever an infection was noted by superficial inspection or on removal of stitches or at any dressing, this was recorded at the time and not retrospectively These observations in the ward were usually made by the ward sister in the course of her dressing rounds, and one useful means of immediate recording was to make a small symbol on the temperature chart at the bedside Routine checks on the methods of assessment and consistency of recording were made by the surgeons in charge of the investigation

When a patient was transferred to a convalescent home or other hospital, a second form, identical with the original, was filled up separately and independently by the doctor at the receiving hospital or home Thus duplicate records were kept for these transferred patients, and in this way it was possible to have a check on all wounds and to ensure proper follow-up

Where a second operation on the same patient involved a fresh incision, a separate form was completed for each operation There were 20 second operations, representing 2 8% of the total records

Multiple wounds at one operation were recorded for 12 cases To avoid difficulties in the analysis, these were regarded as single wounds, and only one form was completed for each case This study covers, in all, 708 wounds

After final discharge of the patient with his wound soundly healed (usually at six weeks), the information was transferred to Powers-Samas punch cards for analysis

Criteria of Assessment

In this investigation the wound state was assessed under two main headings and, so far as was humanly possible, uniform criteria were adopted by the participating medical and nursing staffs The first heading concerned the *nature of the wound*, and by this was meant whether the wound at operation was clean, clean but potentially infected, or frankly infected This decision lay entirely in the judgment of the surgeon The "*clean*" wounds were " cold " orthopædic and neurosurgical cases, thyroidectomy, herniotomy, &c In the "*potentially infected*" group were cases of acute non-perforated appendicitis and cases where the gastrointestinal tract had been opened at operation—e g , at colectomy and at gastrectomy The "*frankly infected*" were cases of ruptured appendicitis, abscesses, &c , these cases were dirty at operation and in the event remained so

The second heading dealt with the *degree of infection* in the subsequent wound, and the degree was assessed as none, trivial, moderate, or severe The definition of these terms was as follows *none*, a dry clean wound without redness, *trivial*, redness at the wound edge or stitch holes, *moderate*, definite signs of inflammation, including a little purulent exudate, and *severe*, frank copious pus

Results

The 708 wounds from the four charges—orthopædic, neurosurgical, and two general-surgery—were associated with a wide variety of common operations In table I the records are analysed in terms of " the type of wound at operation ", the " nature of the wound ", and the type of surgical charge

TABLE I—TYPE AND NATURE OF WOUND AT OPERATION

Type of charge	Type of wound			Nature of wound			Total
	Incisional	Accidental					
		Single	Multiple	Clean	Potentially infected	Frankly infected	
Orthopædic	133	—	—	126	5	2	133
Neurosurgical	129	—	—	115	14	—	129
General surgery I	207	13	8	63	152	13	228
General surgery II	211	3	4	124	74	20	218
Total	680	16	12	428	245	35	708
Percentage of all wounds	96·0	2 3	1 7	60 5	34·6	4·9	100

TABLE II—PERCENTAGE INCIDENCE OF INFECTION IN CLEAN WOUNDS

—	Ortho-pædic	Neuro-surgical	General-surgery I	General-surgery II	Total
Wounds classified as clean and not potentially infected					
No of wounds	(126)	(115)	(63)	(124)	(428)
Trivial	3 2	4 3	12 7	13 7	7 9
Moderate	0 8 }0 8	3 5 }5 2	6 3 }11 1	4 0 }4 0	3 3 }4 5
Severe	—	1 7	4 8	—	1 2
Total	1 0	9 5	23 8	17 7	12·4
Wounds classified as clean but potentially infected					
No of wounds	(5)	(14)	(152)	(74)	(245)
Trivial	20 0	35 7	29 6	33 8	31 0
Moderate	— }20 0	7 1 }7 1	15 1 }18 4	18 9 }23·0	15 5 }19 2
Severe	20 0	—	3 3	4 1	3 7
Total	40 0	42 8	48·0	56 8	50 2
All wounds classified as clean at operation					
No of wounds	(131)	(129)	(215)	(198)	(673)
Trivial	3 8	7 7	24 6	21 2	16 3
Moderate	0 8 }1 6	3 9 }5 5	12 6 }16 3	9 6 }11 1	7 7 }9 8
Severe	0 8	1 6	3 7	1 5	2 1
Total	5 4	13 2	40 9	32 3	26 1

96% of the wounds were incisional The 28 accidental wounds were confined to the two general-surgery charges 63% of the wounds were from the two general-surgery charges, wounds from the orthopædic and neurosurgical charges represented 19% and 18% respectively

60% of the wounds (428) were classified as clean and free from potential infection at operation, 35% (245) were clean at operation but were regarded as potentially infected, and 5% (35 wounds) were frankly infected In both the orthopædic and neurosurgical charges most of the wounds were clean and were *not* regarded as potentially infected Most of the wounds in general-surgery I were classified as potentially infected, whereas in general-surgery II most of the wounds were clean

The difference in the proportion of clean wounds regarded as potentially infected in the two general-surgery charges suggest that there might have been differences in the criteria of assessment, because largely the same kind of surgical work is done in these charges However, we believe that the assessments were fair, otherwise one would have expected that the clean wounds in general-surgery II, where they were in the majority, would have carried a higher infection-rate than the clean wounds in general-surgery I, where they were in the minority Table II shows that this was not so, and in the analysis of the results the figures from the two general-surgery charges can therefore be merged

The main results of the investigation are summarised in table II The 35 wounds which were frankly infected at operation (see table I) and which continued to be septic until eventually healed may be excluded, leaving 673 wounds which were clean at operation and thus at risk to subsequent infection

The incidence of infection is expressed as a percentage for wounds classified by the surgeon as clean and not potentially infected, for wounds classified by the surgeon as clean but potentially infected, and for all clean wounds The number of wounds in each group is shown in brackets

26 1% of the 673 clean wounds were found to be infected at some time after the operation The infection was recorded as trivial in 16 3%, and too much emphasis need not be given to these trivial infections, because redness at the stitch holes and wound margin might well arise from necrosis by suture material rather than from bacterial infection Principal attention will therefore be given to wounds which were seriously infected, and for the purpose of this investigation the moderate and the severe infections are grouped together under the term "serious"

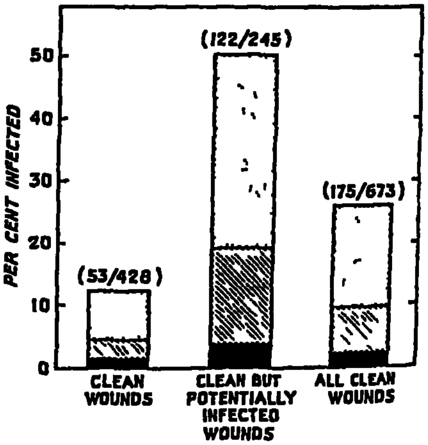
TABLE III—INFECTION-RATES IN DIFFERENT CHARGES

Charge	Wounds	Serious %	Trivial %	Total %
Orthopædic	131	1·6	3 8	5 4
Neurosurgical	129	5 5	7 7	13 2
General surgery I	215	16 3 }13 8	24·6	40·9
General surgery II	198	11 1	21 2	32 3
Total	673	9 8	16 3	26 1

7 7% of the 673 clean wounds (which should not have become infected) showed a moderate degree of infection, and 2 1% became severely infected The overall incidence of serious wound infection in this series, a combination of these two percentages, is therefore 9 8%

Table III summarises the infection-rates in the different charges detailed in table II The incidence of serious infection in the orthopædic charge was relatively low (1 6%) and in the neurosurgical charge rather higher (5 5%), whereas in the general-surgery charges taken together it was as high as 13 8% In this respect the general-surgery charges overweigh the others, and they are responsible for the high average infection-rate

In the potentially infected clean wounds the incidence of serious (i e, moderate or severe) infection was 19 2% (fig 1) In the other clean wounds the incidence of serious infection was only 4 5% The potentially infected clean wounds therefore had an infection-rate more than four times that of the other clean wounds In all four types of charge infection was more common in the potentially infected wounds



Infection in 673 clean wounds operated on in Edinburgh Royal Infirmary: stippled, trivial (redness at wound edge or stitch holes); *hatched*, moderate (signs of inflammation, including a little purulent exudate); *black, severe (frank copious pus)*

Discussion

Colebrook (1955) pointed out how few were the data on which to base an opinion on the incidence of infection in clean wounds, and he suggested that "it would be a salutary thing if one or two of our larger hospitals were to carry out a combined clinical and bacteriological follow-up of all their clean surgical cases over a period of, say, a year" Similar views were expressed by *The Lancet* (1957)

We estimate that the incidence of serious infection in these 673 clean wounds from the Edinburgh Royal Infirmary during this three-month period in 1956 was 9 8% There was an additional 16 3% of trivial infections, making a total of 26 1% As has been said, we do not lay much emphasis on these trivial infections, because many of them may have been primarily due to stitch necrosis, and we prefer to focus attention on 9 8% serious infections This is the average from four surgical charges—two general-surgery and two specialised charges We

TABLE IV—INFECTION-RATES IN DIFFERENT HOSPITALS

Reference	Hospitals	Year	No of wounds	Serious %	Trivial %	Total %
Meleney (1935)	Presbyterian Hospital, New York	1925 1926 1933	558 1132 1053	4·0 4·0 1·1	10·0 11·0 3·6	14·0 15·0 4·8
Howe (1954)	Massachusetts Memorial Hospitals Boston	1953	429	4·6	2·5	7·2
Clarke (1957)	Bristol Royal Infirmary	1953	382	6·5	7·1	13·6
Present series	Edinburgh Royal Infirmary	1956	673	9·8	16·3	26·1

think it probable that the average would have been higher still if all six general-surgery charges of our hospital had been included in the survey, and not just the two of this study, because infection was much more common in the general-surgery cases.

Our survey covers a representative selection of the wounds of the public wards of the Edinburgh Royal Infirmary (there are no private patients), and the incidence of serious infection found in this series appears to be higher than that generally recorded. Complete comparison with other hospital series is impossible. In other series there is generally no mention of the criteria of assessment and no indication whether trivial infections have been included or not. The occasion, or time, after operation when the wound is inspected may have a bearing on the degree of infection discovered and recorded, but this is not commonly reported. The figures presented here refer to the most severe of the different degrees of infection which may have been observed for the same wound. Furthermore, realistic comparisons with the figures for other hospitals is impossible because the type of work done in these hospitals is unknown and may differ widely.

With these reservations in mind it is interesting to compare our results with certain studies where the criteria of assessment at least appear to have been similar to our own (table IV). The Edinburgh figures are seen to be higher, both for trivial and serious infection, compared with Meleney's (1935) pre-war series for the Presbyterian Hospital of New York, Howe's (1954) figures for the Massachusetts Memorial Hospitals of Boston, and Clarke's (1957) series for the Bristol Royal Infirmary.

The infection-rate in the Edinburgh Royal Infirmary is indeed a serious matter, and the surgeons and the board of management have taken cognisance of it and are improving the design and equipment of our operating-theatres. Apart from equipment and technique, the other factor responsible for our infections is the type of work done by our general-surgery charges. These charges have an abnormally high infection-rate because they deal with emergencies and accidents in addition to doing "cold" surgery. There are six general-surgery charges, each with its own operating-theatre, and one day a week they take it in turn to admit emergencies from a population of about a million. There is no separate accident service, therefore not only abdominal emergencies but also road accidents and fractures have to be admitted. Personal experience leads us to believe that accidental wounds are not particularly infectious, and an ischiorectal abscess or a ruptured appendix is more likely to infect other cases than is a road accident. However, the effect of a busy "waiting day" is to disrupt the sterility and efficiency of a "cold" operating-theatre.

We believe that the great majority of our infections originate in the operating-theatre, and that only a minority are cross-infections in the wards. We believe this because many of our operation wounds were left without any form of dressing cover and did not become infected subsequently in the wards; further, many of the infections were discovered on removal of the first dressing. Cross-infection, of course, is undoubtedly a serious risk to open wounds and burns.

It might seem that our system of transferring patients to convalescent homes a few days after operation could be partly responsible for development of infection. War-time experience of the danger of a long line of evacuation certainly supports this theory, but in point of fact our analysis did not bring this out. Indeed, very few wounds developed infection at a convalescent home or arrived seriously infected.

It is fair to say that, in spite of our high incidence of infection, the morbidity was relatively low, the mortality from sepsis was nil, and the main effect of the infections was to prolong the stay in bed in hospital. There were 35 deaths among the patients in this series, but in no instance was death attributable to infection from the wound. This was the opinion of the surgeons in the four charges, and it is pertinent to state that they also felt that this three-month period in the autumn of 1956 appeared to be a light one as regards sepsis. There were none of those devastating outbreaks in which every second wound seems to get infected. Similarly, Dr R. E. Verney, physician in charge of nurses, pointed out that, although the staphylococcal carrier-rate in the nurses usually rose during the months of October–March, 1956 seemed to be an exception to this general experience.

It was originally hoped to follow up the wounds in the surgical charges over a complete year, but the labour of recording was found to be too heavy to be borne for this length of time. The main cause of the labour was that the patients were not kept in the same bed until the wound was finally healed. Many of the patients were transferred to convalescent homes a few days after the operation and even before their stitches were removed, and this entailed duplication of records and of observers. However, although the three-month period of this investigation is too short to give a wholly acceptable figure of the general incidence of infection in our hospital, we feel that it does provide a base-line, and we feel that the procedure of collecting the information that we have outlined has provided accurate figures for the four charges concerned. To lessen extra work for the ward staff, we hope to cover a complete year with a modified form of recording.

Summary

For a three-month period, October–December, 1956, all operation and accidental wounds in four surgical charges of the Edinburgh Royal Infirmary were carefully followed up.

Of 708 wounds, 35 were already seriously infected at operation and remained so. Of the other 673 clean wounds 60·5% were regarded as absolutely clean and 34·6% as potentially infected.

The incidence of serious infection in the 673 clean wounds was 9·8%. There was an additional 16·3% of trivial infections.

The two general-surgery charges showed the highest rate of serious infection (13·8%), the neurosurgical charge the next, and the orthopædic charge the lowest.

In comparing the infection-rates in different hospitals consideration should be given to the criteria of assessment of infection, the number of wounds that are potentially infected, and the type of surgical work done.

Possible sources of wound infection in the Edinburgh Royal Infirmary are discussed.

Acknowledgments are gratefully made to the surgeons, doctors, and sisters in the Royal Infirmary and the associated convalescent homes, who cooperated in this inquiry and kept their records with care and precision The surgeons in charge of the four surgical charges were Prof N M Dott, Prof Sir Walter Mercer, Mr T McW Millar, and Mr W A D Adamson We also thank Dr S G M Francis and others of the administrative staff of the Royal Infirmary for their cooperation and assistance, Dr J H Bowie for bacteriology and advice, Prof J H F Brotherston, of the department of public health and social medicine in the University of Edinburgh, for statistical facilities, and Miss A Stephen for statistical calculations

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THE UNFORGIVING MINUTE IN OBSTETRICS

Thoughts on Strategy and Tactics *

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ANTENATAL care, however diligent, has its limitations It will be fruitless if, for example, the mother dies through delay in removing a retained placenta or the child is born dead because the practitioner, through lack of experience or want of confidence, has not applied forceps to terminate a second stage which lasted too long

In obstetrics, as in battle, no amount of well-prepared strategy will avert defeat from a grave tactical error or from unimaginative failure to seize the unforgiving minute Good antenatal care cannot be too strongly advocated, but to save a life in a tight corner something more may be needed

In this country of late years administrative changes have fostered the idea that midwives, general practitioners, and consultants have separate and distinct roles This has perhaps obscured the simple fact that they have one role in common—to practise skilled obstetrics whenever the occasion arises

As to what in fact constitutes " skilled obstetrics " opinions can still differ considerably, and I shall therefore state my own views on some controversial situations

PROLONGED PREGNANCY

Many, including myself, believe that a certain small number of stillbirths occur simply and solely because pregnancy has been allowed to go appreciably beyond the normally accepted span of 273–280 days In primigravidæ prolonged pregnancy seems to be associated significantly with disproportion, and its management often resolves itself into dealing with this complication In my opinion, whenever labour is 7–10 days overdue, the case should always be reviewed with a consultant

In primigravidæ—particularly elderly ones—if the presenting part is high, and if there is some associated hypertension and the cervix is still unripe, surgical induction is unsuitable Further delay must then become the full responsibility of the consultant

In multigravidæ so-called ageing of the placenta is said to cause fœtal anoxia that may prove fatal before, or more commonly during, labour This explanation is still contested, but at any rate it seems that a postmature infant is more likely to be stillborn if delivery is complicated by application of forceps or even by undue delay in the second stage followed ultimately by normal delivery These are deviations that would not normally be disastrous to infants born at term In a woman whose pregnancy seems to have continued well beyond its normal span, if the cervix is ripe, and the examining finger judges that artificial rupture of the membranes may easily be done, then it should be done In these circumstances labour usually begins soon after induction, suggesting that the procedure has been correct and properly timed

But I must say again that the alleged risks of postmaturity are still sub judice, and that some obstetricians think any interference essentially meddlesome

PLACENTA PRÆVIA

A dozen years ago Macafee [1] pointed out that very many cases of placenta prævia can safely be treated conservatively in hospital until the pregnancy is well advanced, and that if this is done many more live infants will be born

Cases of central or near-central placenta prævia are now being treated by cæsarean section, and the rules laid down by Sir George Makins [2] in the first world war for the treatment of secondary hæmorrhage seem particularly apt

> " Direct ligature of the bleeding spot proved the safest and most effective method Force-pressure and plugging both proved useful where direct ligature was impracticable, and formed the last resorts of surgery "

In the case of the uterus direct ligature implies emptying the uterus expeditiously, so that the normal living ligature mechanism of the interlacing musculature may have full and unrestricted effect on the uterine blood-vessels and sinuses It has taken us rather a long time to learn that plugging of the vagina and pulling down a leg are essentially unsurgical and never likely to be widely successful

PROLONGED LABOUR

Obstetric units vary considerably in their assessment of when true labour has become prolonged, but the old adage " never let the sun set twice on a labour " has a good deal to commend it

The general practitioner carries a heavy responsibility in cases of prolonged labour He often knows the background of the patient better than the consultant does, and in this type of case the advice of an experienced family doctor should seldom be rejected Nor can a responsible general practitioner ever think much of the notion that " even if a woman does lose her first child she can always have another "

I may add that in these litigious days a husband is ultimately going to bring an action against a doctor for unnecessary and avoidable delay in bringing labour to an end—in a case where, for instance, the baby was stillborn or the mother died or developed a vesicovaginal fistula The courts may yet agree to admit such a petition, though proof would undoubtedly be difficult

RETAINED PLACENTA

Sheehan [3] has done much to focus attention on the true nature of so-called obstetric shock He has shown convincingly the dangers of retained placenta and has urged removal after one hour It is also important to remember that in some of these cases, even in the absence of severe bleeding, the patient deteriorates merely because the placenta is still within the uterus (Not everyone agrees with this)

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* Extracts from a lecture given to the Liverpool Medical Institution in 1956

[1] Macafee C H G *J Obstet Gynæc Brit Emp* 1945, 52, 313
[2] Makins G H *History of the Great War Medical Services Surgery of the War*, Vol II, p 181 H M Stationery Office 1922
[3] Sheehan, H L *Lancet*, 1940 i, 1

Anæsthesia for manual removal of the placenta should be light There is great danger in inducing deep anæsthesia for a forceps delivery, and perhaps again a little later in a vain attempt to express the placenta by Credé's method, and maybe yet a third time, after several hours, for manual removal of the placenta This can be disastrous

Any obstetrician—consultant or practitioner—who embarks on a forceps operation should be technically prepared to go on to remove the placenta There is much to be said for coincident manual removal of the placenta immediately after the forceps extraction, during the same anæsthesia, unless the placenta can be readily expressed after the routine intravenous administration of ergometrine

BREECH PRESENTATION

At least some of the bad results obtained outside hospital in cases of breech presentation are due largely to insufficient help and poor anæsthesia To perform a breech extraction comfortably, one needs plenty of good assistance, a competent anæsthetist, proper surgical anæsthesia, a nurse assistant, and a generous episiotomy Given these, with careful antenatal assessment of fœtal size and routine X-ray pelvimetry, breech delivery loses quite a few of its fears But a fair proportion of primigravidæ—possibly 12%—will require elective cæsarean section

The use of external version under anæsthesia is debatable Occasionally a stillbirth results from this manœuvre, and if, besides the abnormal presentation, there are any subsidiary reasons why the uterus might be emptied abdominally as a precaution, then it certainly seems unwise to attempt an antenatal procedure that is itself known to carry some risk of placental separation

CÆSAREAN SECTION

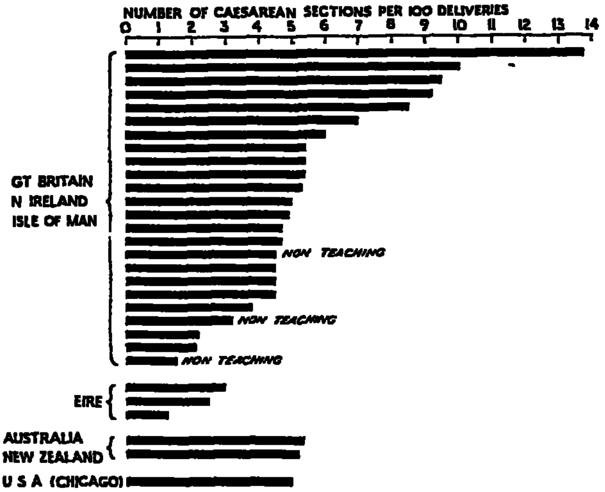
Here I show, in the table and figure, the cæsarean-section rates from several teaching hospitals in Great Britain, the Commonwealth, Eire, and the United States of America These are a matter of importance not only to the consultant obstetrician but also to the general practitioner, for, when he is in sole charge of his patients at the onset of labour, he is the person who does or does not take steps to initiate the operation

INCIDENCE OF CÆSAREAN SECTIONS

	Marshall [4] 1943–47	Corbett 1951–55
No of deliveries	125,179	329,822
No of cæsarean sections	7,762	16,472
Incidence	6 2%	5 0%

A 5% yearly cæsarean section rate represents a very slight downward trend in comparison with the figure given in the survey made almost ten years ago (Marshall 1949) That survey covered far fewer hospitals than does the present one If the figures for Marshall's group of hospitals for 1951–55 were extracted from the present figures they would show a yearly section-rate of 6%—i e , no change since the period 1943–47

On indifferent judgment and inadequate clinical sense may well depend the bad odour in which cæsarean section is often held A speaker at the 1955 conference on general-practitioner midwifery convened by the College of General Practitioners [5] referred to it as a " dangerously safe " operation What he probably meant was that it was often done unnecessarily and too lightheartedly, and that, like every other abdominal operation, it carries some risk Certainly, if it is done too late in labour, the risk is greatly increased The danger, I think, really lies in prolonging labour beyond reasonable limits



Yearly cæsarean-section rate (i e , average yearly rate for 1951–55) as percentages for 30 hospitals, mainly teaching

Imprudent deferment of cæsarean section causes a steep rise in the risks of postoperative peritonitis Bell,[6] in a recent paper to the South African Obstetrical Society, made the following statement

> " In reviewing the present position of cæsarean section it is satisfactory to note that Marshall's paper (1949) was not followed by a wild orgy of sections as predicted by some of those who joined in the discussion of his paper My own memory recalls more women on whom I regret not doing a cæsarean than those where the operation might have had slender indications "

Cæsarean-section rates vary, sometimes greatly, from one centre to another No consultant obstetrician can allow his judgment continually to be impeded by having to keep his section-rate " respectably " low He must on each occasion follow what seems to be the proper course and must accept responsibility whenever the need arises Quite clearly no such thing as an orgy of cæsarean sections will ever take place, and the rates must vary in different centres for reasons that are for the most part obscured in formal reports

OBSTETRIC ANÆSTHESIA

In 1956 the *British Medical Journal* [7] drew attention to the alarming frequency of deaths under anæsthesia, and to their relative frequency in the practice of midwifery The dangers of inhaling vomit have always been known, but Jeffcoate's [8] observation that " in forceps delivery the use of general anæsthesia represents a greater hazard than the obstetrical manœuvre " stands out with disquieting prominence and arresting clarity There seems little reason to doubt that, in general-practitioner midwifery, chloroform is still fairly widely used Is it sufficiently realised in our profession that, for operative vaginal delivery, local anæsthesia offers an always safer and often better alternative to the general anæsthetic ?

Grateful acknowledgment is made of the kindly cooperation of friends and colleagues in this country and abroad who have supplied material from which the statistics cited here have been compiled.

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[4] Marshall C. M XIIth British Congress of Obstetrics and Gynæcology Introductory Papers, 5 1949

[5] Supplement to the college's *Newsletter* no 10, p 28

[6] Bell, A Personal communication

[7] *Brit med J* 1956, ii, 868

[8] Jeffcoate, T N A. *ibid* 1953, ii, 951

THE SUPPLEMENTARY ESTIMATES

According to the Supplementary Estimates [1] published on Feb 4, about £9 million more will be needed in the current financial year for the National Health Service in Great Britain (£7½ million for England and Wales and £1½ million for Scotland) About half this sum will go to the hospital services Together, the hospital boards need rather more than £5½ million extra, mainly to meet increased remuneration, prices, and National Insurance contributions (The last item offers a fascinating glimpse of financial give-and-take between Government departments) These supplements are to some extent met by the saving in England and Wales of about £1 million which the regional hospital boards (but not the teaching hospitals) are expected to show on their capital accounts

The pharmaceutical services will need a supplement of £2½ million The fall in the number of prescriptions has not been sufficient to offset the higher average cost per prescription, and it has also meant a shortfall in payment by patients in England and Wales of £1,099,000 In the estimates for England and Wales an extra £380,000 is provided for the purchase of poliomyelitis vaccine from Canada and the United States

The Ministry of Health itself has a supplementary estimate for £405,000 The National Milk scheme needs an extra £1,150,000, but this is almost offset by an expected saving of £1,130,000 on other welfare foods The extra money needed by the milk scheme is said to be due to the fact that people are using more liquid milk instead of National Dried Milk

Public Health

RESPONSE TO POLIOMYELITIS VACCINATION

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CHILDREN in Iceland were vaccinated against poliomyelitis in the autumn of 1956 American vaccine injected subcutaneously and Danish vaccine injected intradermally were used at the same time in the same localities

This gave an opportunity *for measuring antibody in* comparable groups of children after both types of vaccination The effects of the two methods were compared by means of *a survey in two villages, and an* unexpected difference was found between the responses of the children in the two outwardly similar localities, irrespective of whether they *had received the American or* the Danish vaccine

A brief explanation of recent poliomyelitis history in *Iceland is needed to put our findings into focus*

In 1955 an extensive epidemic of type-1 poliomyelitis had spread over Iceland as shown in fig 1, which is based on measurements of *type-1 antibody in children after the epidemic* The distribution of type-1 antibody agrees well with the distribution of reported clinical cases in 1955 with two exceptions

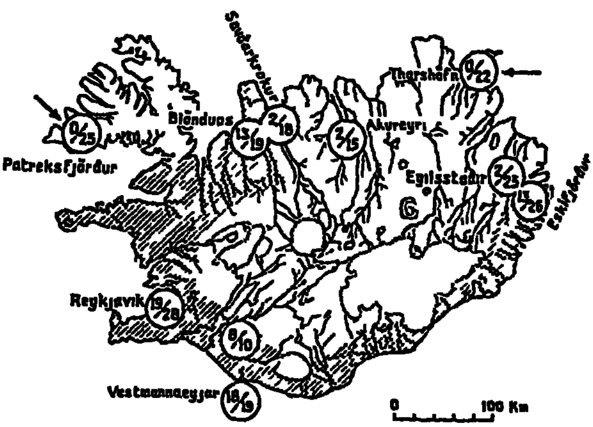

Fig 1—Map of Iceland showing area involved in 1955 poliomyelitis epidemic (hatched) Figures show number of children with type-1 antibody out of number tested in various areas

There had been outbreaks of Akureyri fever (epidemic neuromyasthenia) (Sigurdsson et al 1950, Poskanzer et al 1957) in two small towns, Patreksfjördur and Thórshöfn (indicated with arrows on the map), outside the type-1 epidemic area during and after the poliomyelitis epidemic (table I) These outbreaks were provisionally *registered* as poliomyelitis, though it was recognised from the beginning that they were not poliomyelitis but Akureyri fever This diagnosis was supported by the fact that poliovirus could not be recovered from these cases No antibody to type 1 was found in children in these two communities after the outbreaks (out of 25 children in Patreksfjördur and 22 in Thorshöfn) This is a clear indication that these outbreaks were not caused by type-1 poliomyelitis virus

The other discrepancy between the distribution of registered cases and the distribution of type-1 antibody in children after the outbreak is that antibody was *found in three localities*—Blönduos, Vestmannaeyjar, and Eskifjördur—on the fringe of the epidemic area, though no clinical disease had been reported there

TABLE I—REGISTERED CASES OF AKUREYRI FEVER IN PATREKSFJÖRDUR (1382 INHABITANTS) AND THÓRSHÖFN (780 INHABITANTS)

—	—	1955			1956			
		Oct	Nov	Dec	Jan	Feb	March	April
Patreksfjordur	non paralytic	2	27	35	32	9	3	0
	paralytic	0	9	10	6	2	0	0
Thórshöfn	non paralytic	0	0	10	30	28	11	17
	paralytic	0	0	1	9	7	1	0

Investigation

A survey of antibody to all three types in children under 10 years of age was carried out *before* vaccination was begun On the basis of that survey it was decided to test the efficacy of the two types of vaccine in children in two communities outside the area of the 1955 type-1 poliomyelitis epidemic, Thorshofn and Egilsstadir, in the North East of Iceland

In Thorshöfn (a district with 780 inhabitants), from December, 1955 to April, 1956, 18 paralytic cases and 96 non-

TABLE II—ANTIBODY IN CHILDREN UNDER 9 YEARS, BEFORE VACCINATION

—	No of children	No with antibody to type		
		1	2	3
Thórshöfn	22	0	1	5
Egilsstadir	25	2	0	6

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[1] 1957-58 Supplementary Estimates Civil Estimates and Estimates for Revenue Departments H M Stationery Office Pp 179 11s 6d

paralytic cases of Akureyri fever had been registered. This is an incidence of 14 6% But, as table II shows, the prevaccination poliomyelitis antibody status was in fact very similar in Thórshöfn and Egilsstadir

Only children without detectable previous antibody to any type were included when the results of vaccination were being tested About half of the children in each place were inoculated with Danish vaccine and the other half with American vaccine Fig 2 shows the titres observed in the children two months after the second injection of American or Danish vaccine The two types gave comparable rise in titre after the second injection, but the results were rather poor on the whole

The interesting fact emerged, however, that the rise in antibody titre differed much according to the place of residence, irrespective of whether Danish or American vaccine was used Fig 3 shows that there was only a slight rise in antibody to type 3 and type 2 in Egilsstadir but a relatively good rise in Thórshöfn We have tried to look for extraneous factors, connected with the vaccination, which might explain the different response in the two groups of children We have found no such explanation, and we assume now that the difference lies in the children themselves, or in other words that the children in the two localities varied systematically in their responsiveness to vaccination with type-3 and type-2 poliovirus

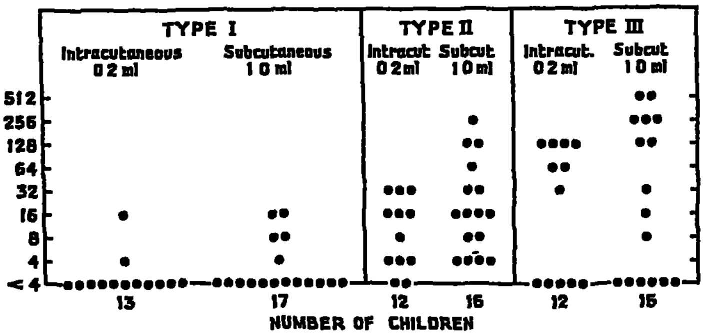

Fig 2—Titres in 30 vaccinated children after second injection

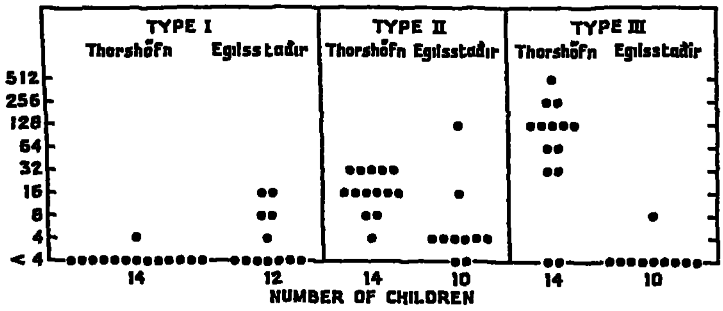

Fig 3—Titres after second injection in Thórshöfn and Egilsstadir

We report this to suggest that other factors than detectable prevaccination level of poliomyelitis antibody may influence the response of a given population to vaccination, and that perhaps previous immunological experience with Akureyri fever may be such a factor

Summary

The responsiveness of children to vaccination against poliomyelitis varied greatly in two separate localities in Iceland

In one isolated locality, without previous history of poliomyelitis, antibody rise to all three types was extremely poor In another isolated locality the response to types 2 and 3 was much better This second locality had recently suffered a severe outbreak of Akureyri fever

This experience seems to suggest that other factors than a detectable level of antibody may influence the response of a given population to poliomyelitis vaccination

The remarkably good antibody response after Salk vaccination often observed in children without previous antibody might perhaps in some cases be explained by the existence of basic immunity acquired through a related infection

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Acute Respiratory Disease in Babies

The Ministry of Health reports that since Jan 20 an increase has been observed in the number of babies in London needing admission to hospital Since that day between a third and a half of all admissions arranged by the Emergency Bed Service on account of acute respiratory illness has been of children under 5, and of these most have been from 3 months to 2 years old There has been no corresponding increased need for hospital beds for older patients There are indications of a similar situation in Birmingham

The babies usually have a history of a cold for two or more days followed by deterioration, often rapid, with evidence of disease of the lower respiratory tract The more severely ill children have been restless and cyanosed and have shown intercostal recession on inspiration and other evidence of respiratory-tract obstruction, but signs of consolidation have not been prominent There have been few deaths In many cases oxygen therapy has been essential, whereas antibiotics do not seem greatly to have affected the course of the illness though they may have helped to avert secondary infection No evidence has been obtained to suggest a bacterial cause

In November, 1953, outbreaks resembling the present one were observed in London, Liverpool, and Manchester,[1] and another outbreak in Sunderland in 1953 [2] seems very similar Efforts to show that the illness was due to influenza or other viruses were unsuccessful, and the aetiology is still unknown Additional information might be obtained if outbreaks were reported to medical officers of health as soon as they were recognised

Clean Air Act

Some provisions of the Clean Air Act are already in force—e g, powers enabling local authorities to establish smoke-control areas One of the stumbling-blocks in certain areas—the reluctance of coalminers to buy smokeless fuel when they receive free concessionary coal [3]—has been overcome by the National Coal Board's agreeing to buy back concessionary coal from any miners whose home is in a smoke-control area

By order of the Minister of Housing and Local Government, the remaining provisions of the Act will come into force on June 1 Under these provisions the emission of dark smoke from chimneys will be banned and emission of grit and dust minimised A fine of up to £100 will be the penalty for the emission of smoke darker than shade 2 on the Ringelmann chart This ban applies to all chimneys, but domestic chimneys rarely exceed shade 2 Certain defences are allowed—that suitable fuel was unobtainable, that a furnace was being lit from cold, or that the apparatus had failed unforeseeably All practicable steps must be taken to minimise the emission of grit and dust from existing furnaces (except small domestic boilers), and all new large furnaces will have to be equipped with plant, approved by the local authority, to arrest grit and dust

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[1] Ministry of Health Annual Report of the Chief Medical Officer, 1953, p 45

[2] Haycock J B, Noble, T C. *Brit med J* 1956, i, 438

[3] *Times*, Jan. 18, 1958

Progress with Detergents

In some places masses of foam floating on rivers and canals are as familiar a sight as advertisements for detergents are everywhere, and one town has complained of foam from a weir blowing along its streets This is not only spectacular but also possibly dangerous because masses of foam seriously reduce the chances of rescue if anyone falls in the water The *Standing Technical Committee on Synthetic Detergents*, set up in January, 1957, has now issued a progress report,[1] in which it points out that the rapid increase in the use of surface-active material has levelled off since 1953, in 1956 the United Kingdom figure was 41,000 tons, of which 34,500 tons was used in the home

The committee is considering the effects of detergents on the essential aeration processes at sewage works and the effects on the effluent of antifoaming agents used there The Water Pollution Research Laboratory is investigating the toxicity of detergents to fish

The committee is satisfied that the manufacturers are seriously trying to overcome the disadvantages of their products by finding a substitute that can be readily eliminated by the present sewage methods

The Registrar General's Civil Tables

The Registrar General has issued the second volume[2] of his review for 1956

The marriage-rate was 15 7 per 1000 population (16 0 in 1955), more than a fifth took place in March, doubtless for fiscal reasons In the 352,944 marriages, 30,844 men and 113,494 women were under 21 years old The commonest age for marriage remained 23 for men and 21 for women The birth-rate (15 6 per 1000) was the highest since 1950, illegitimate live births were 4 8% of all live births (4 7% *in the previous three years) There were 700,355 live births, 8660* confinements resulted in twins, 78 in triplets, and 1 in quadruplets The number of new petitions filed for divorce increased from 28,314 in 1955 to 28,426, the first rise since 1951, the average number in 1951–55 was 32,168

Medicine and the Law

Guilty but Insane

THE Homicide Act, 1957, introduced the defence of diminished responsibility in order to provide for cases where the mental condition of the accused does not amount to insanity as defined in the McNaughten rules In general, it will no doubt be easier to prove diminished responsibility than insanity The McNaughten rules remain in force, however, and there may be cases in which the nature of the medical evidence is such that a plea of insanity will be the more appropriate defence In other words, the legal definitions of insanity and diminished responsibility involve a difference of kind as well as degree

The McNaughten rules were in fact applied in a murder trial at Leicester Assizes last week, in which *a man aged 24 was charged with the murder of an 8-year*-old boy Medical evidence was given that the accused was suffering from schizophrenia and did not know at the time that his action was wrong He was found guilty but insane[3]

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[1] Ministry of Housing and Local Government Progress Report of the Standing Technical Committee on Synthetic Detergents H M Stationery Office 1958 Pp 8 6d

[2] Registrar General's Statistical Review of England and Wales for the Year 1956 Part II Tables, Civil H M Stationery Office, 1958 Pp 180 7s 6d

[3] *Times*, Feb 4, 1958

In England Now

A Running Commentary by Peripatetic Correspondents

FOR a great part of mankind, some kind of creative activity is essential for a satisfying life Many men and women, however satisfying their professional work may appear, cannot rest unless they produce works of art as well, and painting is a tranquilliser shared by many, including heads of States and doctors Tranquillity is the keynote this year at the Medical *Art Society,*[1] *as Sir Philip Manson-Bahr's Cologne Cathedral*, Dr E J E Topham's *Isleworth*, and Dr Isabel Wilson's *Clifton Bridge* exemplify Mr R T Payne's *Nude* is a very pleasing and simple composition, while Dr T Anderson's water-colour *Orchard, Impington* is tranquil but also one of the most original and lively pictures in the show

Such a spark of liveliness is a feature much missed in most of the pictures Anyone lucky enough to have seen the recent film of Picasso at work must have been impressed by the deceptive ease with which each picture seemed to be created But to produce such masterpieces there is need not only of phenomenal talent (and many of the society's members have much talent) but also of phenomenal vitality On the whole the sculpture—especially Dr G Konstam's *Fallen Horse*—is more vital than the paintings, but Dr Ph Tuttnauer again has some fine individual canvases that speak of an exuberance to be expressed only by painting Dr Sylvia Payne contributes a portrait that, though unattractive, is disturbing and interesting, and Dr G E Loxton a flower-piece of notable surface texture Mr B N Brooke, besides a bold water-colour, *Lock at Lapworth*, has the most outstanding picture of the exhibition—an oil called *Calvary* In the dark background are three dry empty crosses near the summit of a hill, in the foreground unfold two heavy succulent plants, one apparently still in the ground, the other uprooted and drifting One can only guess at the meaning of the symbolism here, but the *composition and colouring are as accomplished as the whole* picture is vital

* * *

Our chest clinic is held twice a week and many of our African patients attend from as much as 200 miles away They are treated on P A S powder and isoniazid tablets, and one of our difficulties is to ensure that back home they take the correct dose, *for the flat wooden spoons used by the African peasant* are unreliable measures The problem has been solved by my chief, who observed that even in the most remote parts of the country every duka, as a small shop is called here, carries the ubiquitous advertisement, "Drink Dash's Cola" He worked out that 5 g of P A S fills two bottle-tops with the corks removed So our prescription runs "2 flat Dash's Cola tops P A S powder twice daily"

* * *

I have had an experience which I believe to be unique On a Monday morning, when I should have been in the wards, I drove to the Royal College of *Physicians*, wearing pyjamas and sandals and with my hands as black as the ace of spades It was my husband's final viva in the M R C P examination and the circumstances were extenuating

After leaving him at the door of the college my problem was how to pass the time At first I sat shivering in the car beside a No Parking notice The icy January wind came through the floorboards and caught my pyjamas I was still suffering from this when a policeman, apparently not interested in pyjamas, asked why I displayed last year's licence No sooner had I finished explaining than another policeman appeared and I had to explain all over again I decided that, pyjamas and all, I would have to leave the car and hope for the best about the No Parking notice and last year's licence

My pyjamas were rather gay, so I brought a curl down over my forehead, decided that I would pass for an art student, and walked towards the National Gallery On the way I passed two characters whom I thought looked even queerer than I did, and this gave me the confidence to run up the steps and through the swing doors Once inside I felt less sure of myself It looked so formal, including the arty-ladies selling postcards There were other people, presumably real art students, with curls over their foreheads, but none had hands as black as mine or wore pyjamas However, my confidence rose when no-one stared at me, not even the custodians Obviously this was an everyday occurrence I even managed to forget my plight for a while and to enjoy some of my favourite pictures

---

[1] The exhibition is on display at Walker's Galleries 118 New Bond Street until March 5

By the time I thought my husband might be reappearing I felt almost normal and able to face a walk in Trafalgar Square Near one of the fountains some people stared at me rather offensively, but these, I decided, were tourists in search of local colour Increasingly confident, I walked happily up the west side of the square and peered in at the windows of the college to see if I could see my husband in the moment of agony There was only a man polishing a table, but when I turned round, there, coming towards me, inescapably staring at my pyjamas, my hands, and my curl, was my Chief To give him his due, he gave me a sort of sickly smile

* * *

Last week my hand lighted on an unfamiliar volume erupted in the domestic spring upheaval, a treatise on tobacco-smoking sent for review in 1911 when I was editing my hospital journal It is a depressing work—even to a non-smoker Its gloom is illuminated by a solitary ray of humour, and that unintentional As "*corrigendum* page 56, for *salvation* read *salivation* "

The author traced a more or less direct connection between Sir Walter Raleigh's discovery and his disastrous termination The "so-called soothing weed" was credited with the production of tabes and sterility, for "even the perspiration of a smoker being absorbed by his wife can poison the ovum " The opinion was advanced that the only women who suffer from cancer were the wives or daughters of men who had indulged in tobacco to excess (To appreciate these views at their full value it should be added that the author was a doctor)

After these charges, the inclusion of insanity was a modest expectation Yet I visualised the smoker-reader grinning as he lighted his pipe with a spill from one of the pages, and concluding that so far from tobacco-smoking leading to insanity, there would appear to be abundant evidence that this infirmity results from its abstinence

* * *

I agree with last week's correspondent that many " insomniac " patients are trying to get too much sleep I was once called to one who was lying in bed at 4 p m

' What s the trouble ? '

" I want some sodium amytal '

Can't you sleep ? "

" No "

' What time do you go to bed at night ?

' Oh, I sleep all right at night, it s in the daytime I have trouble "

* * *

A case-record received in the office the other day told of a child that was born with " hypertelevision " Is this another example of a throwback or just plain ATV-ism ?

* * *

In each of us there is an inborn urge to feed birds and animals, an urge that makes us scatter bread to sparrows and to ducks, brings business to the dried-pea vendors at Trafalgar Square, encourages dogs and polar bears to sit up and beg, and leads to occasional warnings at London Zoo that certain animals ought not to be fed

There is a little courtyard in the Inner Temple where a fountain plays (when not afflicted with stricture), where lawyers stroll, or sit and munch sandwiches, and where a perambulator, containing a sleeping infant, carries the placard

PLEASE DO
NOT FEED
FIONA

Letters to the Editor

NEW LOOK IN RESPIRATORY INFECTIONS

SIR,—My purpose is to draw attention to changes in the pattern of chest infections seen this winter in the medical wards of a general hospital—changes which were sudden and unexpected

The rush of chest cases following on the much-publicised Asian flu did not materialise, and the first intimation that anything was amiss was when a male, age 54, being treated in hospital for diabetic neuritis died in three days, and at necropsy the cause of death was an acute staphylococcal pneumonia This occurred in October, and although there were 3 more staphylococcal pneumonias admitted in this month, 1 of which was fatal, the real blow did not fall until November and December when 22 patients suffering from staphylococcal pneumonia were treated in my wards The lung infection was so acute and severe that erythromycin or novobiocin was given at once in suspected cases (especially if the sputum was a dirty brown-green colour and non-aerated) without waiting for the laboratory report In this way lives were saved

The clinical picture of the emphysematous patient was that of an acute bronchiolitis with mental disturbance, they were severely cyanosed and there were surprisingly few physical signs in the lungs [1] It was not surprising, therefore, that tracheostomy and suction did not relieve the cyanosis in one patient, and, following this experience, when an older emphysematous patient, aged 72, presented in the same way with extreme cyanosis and semi-coma, we hesitated to advise tracheostomy although his chest was " bubbly " and he could not raise his sputum Instead, we gave erythromycin and within forty-eight hours he was conscious and fairly well oxygenated

In spite of these experiences, the staphylococcus outwitted us in January of this year when it manifested itself as a classical lobar pneumonia in a woman of 32 She died, and in retrospect the anomalous feature was the abundant rales in the affected lung at the height of the illness

The sputum was examined in 62 patients who were admitted to my wards with a chest infection between September, 1957, and January, 1958, inclusive 42 also had chronic bronchitis and emphysema and of these 13 died, 4 of the remainder died Initial examination of the sputum showed non-pathogens in 29, pneumococci in 10, hæmophilus in 10, coliforms in 9, and *Staphylococcus pyogenes* in 11 Subsequent sputum examination of the same patients showed 4 more with hæmophilus, 4 with pneumococci, and 15 with *Staph pyogenes* Only 5 of the staphylococcol strains grown were penicillin-sensitive, and 3 patients who had *Staph pyogenes* in the sputum were clinically well Erythromycin and novobiocin proved to be the most effective drugs against the *Staph pyogenes*, although mycelia of monilia were found in the sputum of treated cases, they disappeared spontaneously

The male patients were nursed in six-bedded wards, and although cross-infection was never proved it was strongly suspected

It may be that the notifiable infectious disease of the future will be *Staph pyogenes* pneumonia and use may again be found for our empty infectious-disease hospitals

One advantage of a personal bronchitis and emphysema clinic, such as I run, is that patients may be admitted to hospital earlier in their infection, but this did not prevent 2 of my patients dying before admission

At our peril will we trust or ignore the staphylococcus, which may use different disguises to deceive us, the other pathogens in the respiratory tract do not appear to be so cunning We should reassess the value of prolonged antibiotic therapy in the chronic bronchitic Nature may not submit to our attack—her mood now is certainly ugly and has left us licking our wounds Let us hope her anger is spent

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[1] Simpson, T *Brit med J* 1954 i, 297

Chase Farm Hospital,
Enfield, Middlesex. THOMAS SIMPSON

THE LIFE FOR ME

SIR,—Dr Richard Cobbleigh's accounts of his progress through the medical jungle are always stimulating reading, the more so as not all of us would agree with his diagnosis of what are false trails and blind ends Even his myths (such as the one in his Widdicombe letter of Feb 8—the "M O H who *still* doesn't believe that G P s exist") throw some light, though only scanty illumination, on some obscure professional mental processes which perhaps merit more study from his newly adopted specialty than they have yet received

Apparently hydrocortisone ointment as a panacea for skins lets us all be dermatologists It is not quite so clear whether E C T as a panacea for mental illness lets us all be psychiatrists, but I hope that as the Cobbleigh Career progresses in this field it will encounter the growing edge which deals with prevention Not a few of his new colleagues have passed beyond empirical treatments like E C T to cope with the more difficult problems of trying to find the psychological factors leading to problem families, juvenile delinquency, neurosis, and behaviour problems And if our Angry Young Doctor-turned-psychiatrist ventures this far he may even once again find himself back in "those Clinics" where the M O H has already extended a warm welcome and an attentive ear to preventive psychiatry

I look forward eagerly to Dr Cobbleigh's reflections on his further progress

J A SCOTT
Public Health Department,
London, S E 1
Medical Officer of Health for the
County of London

BETWEEN GUESSWORK AND CERTAINTY IN PSYCHIATRY

SIR,—I agree most profoundly with Professor Lewis's contention (Jan 25) that, in certain directions, progress in psychiatry requires collaboration between psychiatrists and psychologists Speaking as a person trained in both disciplines, I would like to draw attention to certain mutual irritations which keep the two professions apart By and large, psychologists are more research-minded than psychiatrists and have a better grounding in scientific method, and especially in statistics Speaking for the moment as a psychologist, I would record with deep feeling the fury which psychiatric colleagues can arouse by their ignorance of the significance of a simple statistical technique which should present no challenge to the intellect of anyone who has passed G C E mathematics at O level Therefore, *if psychiatrists are to be acceptable colleagues* to psychologists they must at least learn some simple statistics

If I may now switch to my alter ego, the psychiatrist, he points out that the psychiatrist is more pragmatic than the psychologist Pragmatic is, to him, a more polite term for "not up in the clouds" The psychiatrist wants techniques which will work in the clinical hurly-burly of wards and outpatient departments He has no love for the irritating psychologist who keeps telling him that his pet methods have never been scientifically validated, but never seems to offer an alternative which can be vouched for by science

It should not be beyond the united resources of the two professions to solve this little problem in interpersonal relationships

Long Grove Hospital,
Epsom, Surrey A B MONRO

DUODENAL ULCER AN OBSERVATION

SIR,—Data from several sources have shown an association between blood-group O and duodenal ulcer Cumulative figures have been weighted to confirm this association in a manner appropriate to the varying incidence of blood-group O in the differing communities from which material has been drawn The object of this letter is to draw attention to a phenomenon which appears if ABO blood-group data in subjects with duodenal ulcer are compared with control blood-group data from the same place, counting each observation as a separate and equivalent unit

TABLE I

Place	Source	$\frac{A}{A+O}$ Ratio	
		Control	Duodenal Ulcer
London	Aird et al [1]	0 480	0 368
Newcastle	Aird et al [1]	0 443	0 363
Manchester	Aird et al [1]	0·454	0·425
Denmark	Koster et al [2]	0 520	0·433
Glasgow	Peebles Brown et al [3]	0 375	0 348
Iowa	Buckwalter et al [4]	0·476	0 404
Liverpool	Clarke et al [5]	0 444	0 342
Norway	Westlund & Heistö [6]	0 569	0·470

The A/A+O ratio in controls and of macroscopically proven cases of duodenal ulcer from previously published data are shown in table I and presented graphically in fig 1 There is a significant correlation between the A/A+O ratio of duodenal ulcer subjects and the A/A+O ratio of the control populations

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1 Aird, I , Bentall, H H , Mehigan, J A , Roberts, J A F *Brit med J* 1954, ii, 315
2 Koster, K H , Sindrup, E , Seele, V *Lancet*, 1955, ii, 52
3 Peebles Brown, D A , Melrose, A G , Wallace, J *Brit med J* 1956, ii, 135
4 Buckwalter, J A , Wohlwend, E B , Colter, D C , Tidrick, R. T., Knowler, L A *J Amer med Ass* 1956, 162, 1215
5 Clarke, C A , Cowan W K., Wyn Edwards, J , Howel Evans, A W , McConnell, R B , Woodrow, J C , Sheppard, P M *Brit med J* 1955, ii, 643
6 Westlund, K , Heistö, H *ibid* 1955, i, 847

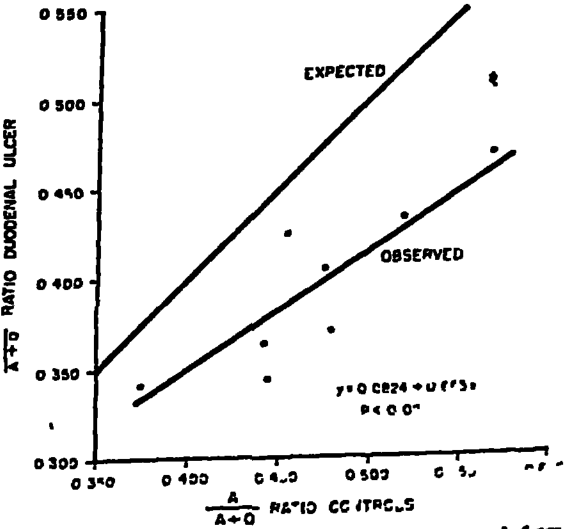

Fig 1—Duodenal ulcer: A/A+O ratio compared with controls from 8 sources.

TABLE II

Place	Source of control blood-group data	*Control blood-group-A gene frequency*	Duodenal ulcer crude male mortality age 60–69 (1951–53)
Norway	Heistö [7]	*0 322*	*3 6*
Denmark	Koster et al [2]	0 283	13 6
U S.A	Hogg and Pack [8]	0 258	18 0
Australia	Simmons et al [9]	0 243	20 3
Scotland	Peebles Brown et al [3]	0 195	34 2

(r=0 823, P < 0 02) The position of the regression line shows the association between blood-group O and duodenal ulcer More interesting is the observation that the association with blood-group O in duodenal ulcer increases as the proportion of blood-group A in the controls increases (χ^2=28 78, N=7, P < 0 001)

One possible interpretation of this phenomenon is that the possession of blood-group A protects against duodenal ulcer, and as blood-group A increases in control populations there is selection against blood-group A in corresponding duodenal-ulcer populations

If such selection does occur, one might expect that with the varying prevalence of blood-group A between different populations, there would also be a reciprocal variation in the prevalence of duodenal ulcer Direct prevalence figures are difficult to obtain, but crude mortality-rates, with their limitations, are available As duodenal ulcer is a predominantly male disease, with the greatest number of deaths between 60 and 70 years, it appears reasonable to compare crude mortality-rates in men of this age-group rather than standardised mortality-rates, provided that the standard of death notification in communities to be compared is also comparable From the figures provided by the World Health Organisation [10] for the years 1951–53 inclusive, the mortality-rates for Australia, Scotland, the United States, Denmark, and Norway can be used Comparison with ABO blood-group distributions will be valid only provided that within each country there are no wide variations in the ABO blood-group frequencies, and for this reason data from England and Wales cannot be included From the blood-group data of the countries cited, blood-group-A gene frequencies have been calculated by the method of Dobson and Ikin,[11] and when they are compared with the selected male mortality-rates from duodenal ulcer (table II, fig 2), an excellent negative correlation exists (r=0 992, P < 0 0001)

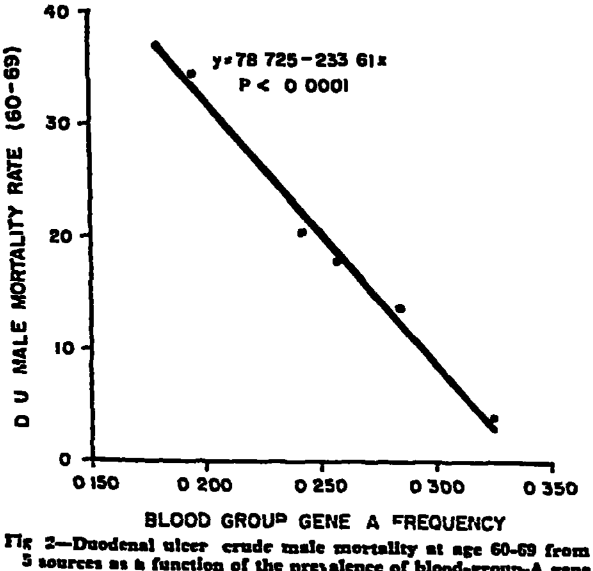

Fig 2—Duodenal ulcer crude male mortality at age 60–69 from 5 sources as a function of the prevalence of blood-group-A gene in a control population

The data will support the hypothesis that blood-group A protects against duodenal ulcer, provided that the inheritance of the disease is not related to ABO blood-groups, and this appears to have been established by Clarke et al [12] It has been shown with gastric diseases [13,14] that the association with ABO blood-groups appears to be related to intragastric site, irrespective of the nature of the disease, and it seems likely therefore that the association between duodenal ulcer and blood-group O may be a similar manifestation of site-susceptibility

From the work of Hartmann [15] the secretor status of an individual appears to determine the amount of blood-group substance present in the duodenal mucosa If blood-group-A substance gives best protection against duodenal ulcer, it would be reasonable to expect that where less material is present there would also be less protection, and this may explain why Clarke et al [12,16] show an excess of non-secretors in subjects with duodenal ulcer These workers hold that blood-group and secretor status are not independent factors in the genesis of the disease, and this receives support from the data of McConnell and Sheppard [17] where the variations from the control ABO blood-group distribution are best shown in duodenal-ulcer subjects who are non-secretors

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B P BILLINGTON

PARADOXICAL ELECTROCARDIOGRAM IN CORONARY EXERCISE TEST

SIR,—Dr Geoffrey Bourne [18] states that he has been unable to find any previous report of the "paradoxical result of an exercise test" Dr Bourne will find a number of examples published in the papers of Alzamora-Castro I have observed this phenomenon rather frequently when ischæmia is responsible for small inverted or diphasic T waves

Actually, in addition to the speculations quoted by Dr Bourne there are two different ways in which the T wave may be paradoxically reversed by exercise—by the occurrence of an injury shift of opposite direction to that of the T wave, and as a result of increase in the rate of repolarisation in ischæmic muscle due to increase in rate A third and spurious mechanism must be considered Even if the electrodes are fastened to the chest, the altered position of the heart, due to respiratory phenomena associated with exercise, changes the position of the electrodes in relation to the heart This may be evidenced by changes in the QRS complexes such as are seen in Dr Bourne's records At times, however, the QRS change is not sufficiently great to be evident Dr Bourne (or anyone) may strap the electrodes to the chest of his patient with diphasic T waves and study the effects of a deep breath and of forced expiration

New Orleans

MANUEL GARDBERG

SIR,—We have read with much interest Dr Bourne's article [18] We have often observed the phenomenon he describes in the cardiological clinic of the Greek Red Cross Hospital (director, Dr C Maroulis) in the past two years, but have not published our observations It is very important to know its prognostic significance, compared with that of the ordinary electrocardiographic response after exercise, and we should very much like to know Dr Bourne's views on this point

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[8] Hogg, L., Pack, G T *Gastroenterology*, 1957, 32, 797

[9] Simmons, R T, Semple, N M, Graydon, J J *Med J Aust* 1951, i, 105

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[13] Billington, B P *Aust Ann Med* 1956, 5, 141

[14] Balme, R H., Jennings, D *Lancet*, 1957, i, 1219

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[17] McConnell, R. B, Sheppard, P M. *Acta genet statist med* 1957, 6, 574

[18] Bourne G *Lancet*, 1957, ii, 1320

Greek Red Cross Hospital,
Athens
MICHAEL MILINGOS

ANTIBIOTIC PROPHYLAXIS

SIR,—May I correct Dr Jhaveri's misapprehension (Feb 1) of the point of my previous letter (Jan 18) The point was not that antibiotics are more toxic than sulphonamides but that their use may cause a state of allergy with the direst consequences if the same antibiotic has to be used later to cure an infection I have never found that sulphonamides, in the doses used as a cover for dental extractions, are toxic or provoke allergy

Secondly, I should explain to Dr Sklar (Feb 1) that I do not use sulphonamides for the treatment of arthritis accompanied by focal sepsis, but solely as a prophylactic measure for a short period before and after an operation dealing with the focus As I said in my letter, I used to prescribe sulphathiazole 1 g 4-hourly for 24 hours before and 48 hours after the operation Recently, however, I have used sulphamethoxypyridazine ('Lederkyn') With this long-acting sulphonamide I have found that 1 g daily, for the same length of time, provides adequate cover

In the 1930s Okell and Elliott[1] found on blood-culture very definite bacteriæmia after tooth extraction, and Fischer and Gottdenker[2] found the same after tonsillectomy Before that I had seen three patients with early arthritis who became completely crippled after the extraction of infected teeth The question now at issue is what is the best drug to render the blood sterile after the influx of potentially infective bacteria? Since sulphonamides are at any rate successful in preventing exacerbation of the arthritis, and by inference rendering the blood sterile, there is no justification for prescribing antibiotics

My thanks are due to Messrs Lederle for a supply of 'Lederkyn'

London, W 1
H WARREN CROWE

CARDIAC ARREST FOLLOWING ELECTROPLEXY

SIR,—This brief account may be of interest, particularly to psychiatrists

A man who had previously had much electroconvulsive therapy had a further treatment in a hospital outpatient department After an injection of atropine 45 minutes before, thiopentone (0 2 g) and suxethonium bromide (100 mg) were given intravenously Having had a convulsion, the patient began to breathe normally, and oxygen was given at first At this stage he was not cyanosed and his pulse was normal

About 5 min later, breathing ceased and the pulse disappeared He was extremely pale and appeared to be dead Auscultation showed that the heart had stopped Nikethamide (2 ml) was immediately given intravenously, and artificial respiration with oxygen given, but without any immediate effect Cardiac arrest lasted at least 3 minutes and probably more There was a sudden convulsive gasp, and as the stethoscope was applied the first beat of the heart was heard, followed after an interval by infrequent irregular beats and then a fast regular rhythm

Respiration was complicated by laryngeal spasm and stridor, resembling croup in a child This was replaced after about 10 min by severe bronchospasm Atropine and then adrenaline were given The patient was unconscious during all this time Eventually he recovered fully and was none the worse for his experience

The significance of this incident lies in its bearing on the occasional mortality associated with electroplexy This treatment is very effective in many cases, but there is still uncertainty about contraindications The use of muscle relaxants has obviated the risk of fractures and excessive exertion in the elderly, but the unpleasant subjective feelings necessitate the use of short-acting barbiturates Both types of drug have been blamed for adding a further risk to a relatively safe treatment

In this case it seems that parasympathetic excitation led first to vagal inhibition of the heart, then to laryngeal spasm, and later to bronchospasm

This case indicates that the dangers of electroplexy may lie not so much in the actual fit, but in the aftermath, when parasympathetic overactivity may inhibit the heart The immediate treatment should be atropine or a similar drug, and it is wise to give it always before treatment

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P J CROWLEY

PHOTOGENIC EPILEPSY

SIR,—I was interested to read the paper by Dr Hutchinson and his colleagues (Feb 1) Recently I saw a patient whose attacks of major epilepsy appeared to be induced by photic stimuli in a rather unusual manner

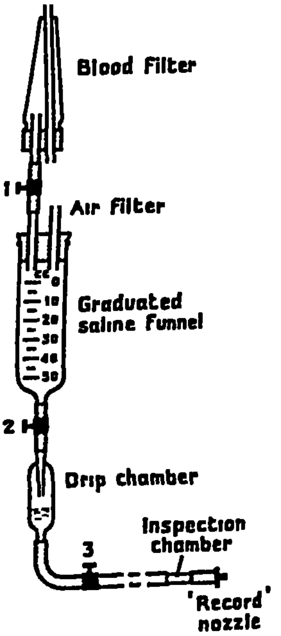
The patient was a man of 27 who was an electrician employed by a television-hire company On two occasions he was called to customers' homes to deal with what proved to be an identical fault as a result of which the screen emitted a rapidly flickering light After a few minutes' exposure he lost consciousness on both occasions He gave no previous or family history of epilepsy, and a year had elapsed between the attacks

Electroencephalographic examination revealed a normal resting record, but during photic stimulation there were a number of brief generalised outbursts of slow activity and spikes suggestive of idiopathic epilepsy

Dryburn Hospital,
Durham
G ISMAY

A BURETTE FOR GIVING INFUSIONS TO INFANTS

SIR,—One of the difficulties that beset those who give intravenous fluids to infants is that of regulating the flow-rate of the infusion accurately In a report on variation in the rate of flow of drip infusions Dr J N Walton described a piece of apparatus which obviates this difficulty[1] Using similar apparatus at the Royal Waterloo Hospital, we have found that it combines the advantages of simplicity and ease of sterilisation



A standard transfusion set is used, with extra long tubing to facilitate the changing and feeding of the infant A burette is incorporated between the blood filter and the drip chamber It consists of a graduated saline funnel (as used for tube-feeding infants) with a two-holed rubber stopper containing two short lengths of glass tubing, one of which acts as an air inlet and contains a plug of cotton-wool as an air filter A gate clamp above and below the burette serve to refill it with fluid each time it becomes empty Another gate clamp below the drip chamber regulates the flow-rate of the drip

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[1] Okell C C Elliott S D *Lancet* 1935 ii 860
[2] Fischer J Gottdenker, F *Wien klin Wschr* 1936 49 177

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[1] Walton, J N *Lancet*, 1947, i 662

The infusion is set up in the usual way, the burette being filled by opening gate clamp (1) Air is then expelled from the system by opening gate clamp (2) to allow the fluid to flow through the tubing When the infusion has been set up and regulated, the gate clamp (3) need not be touched except to readjust the rate of flow of the drip if necessary

Detailed instructions can be given to the nurses as to how often the burette is to be replenished, and hour-to-hour control over the rate of flow of the drip becomes possible.

My thanks are due to Dr B D R. Wilson for his help, and also to Messrs Allen & Hanburys, from whom the apparatus may be obtained 50 ml graduated saline funnels with two-holed rubber stoppers are made by H W Bush & Co of Croydon and are stocked under the number 364 G

St. Thomas's Hospital,
London, S E.1

P C BEWES

TREATMENT OF BREAST CANCER

SIR,—In your leading article of Feb 1, and in Professor Smithers's masterly summing-up last week, the Birmingham figures are mentioned At least two of these figures need explanation

On p 9 of the report,[1] in table 4, survival-rates are quoted where carcinoma of the breast is complicated by pregnancy Here it is stated that where pregnancy occurred after treatment the three-year survival-rate was 73 3% and the five-year survival-rate was 75% Does this, perhaps, include the child?

Bangor

W SKYRME REES

PREMEDICATION FOR GASTROSCOPY

SIR,—Gastroscopic examination is usually carried out under local analgesia, though Goligher and Thornton[2] advocate general anæsthesia, which has a useful place in selected cases

The local agent is a cocaine derivative, and one of the least toxic and most reliable is lignocaine, used in the lozenge form in a dose of 250 mg Anæsthesia is adequate if the tablet is allowed to dissolve in the mouth and the resultant suspension gradually swallowed Viscous lignocaine can also be used, but the injection technique is now rarely used

To prepare the patient for this examination, sedation is necessary and some form of opiate is normally prescribed This is unsuitable for outpatients and has several other disadvantages The commonest combination is morphine sulphate gr $^{1}/_{4}$ and atropine sulphate gr $^{1}/_{100}$, but, in my experience, nausea may occur with considerable "gagging"

In a series of 100 consecutive elective admissions to hospital, the patients were given morphine gr $^{1}/_{4}$ as a test 7 vomited and a further 10 felt miserable with nausea

The incidence of such symptoms, using morphine and atropine was 14% in a series of 250 endoscopies In these, the examination was not only unpleasant to the patient but also difficult for the examiner As various opiates seemed to behave similarly, it was decided to try an alternative

A drug is needed to relieve anxiety without loss of cooperation, to sedate without drugging, to allay nausea and retching, and to enhance analgesia Chlorpromazine hydrochloride, highly successful in producing tranquillity of mind, and its anti-emetic effect in various disorders, seemed worth a trial

It was given intramuscularly, in a dose of 50 mg, with atropine sulphate gr $^{1}/_{100}$ thirty to forty-five minutes before the anæsthetic lozenge, and the effect has been very satisfactory In 200 consecutive examinations, only 5 patients had any significant gagging and feeling of sickness, and all others felt relaxed and unperturbed by the procedure While the number of cases is perhaps small for statistical accuracy, the improvement in the comfort of the patient has been striking No complications have been seen, and the technique seems satisfactory for outpatients Toxic effects after a single dose are extremely unlikely and have not been observed.

Chlorpromazine hydrochloride is therefore recommended as a safe and reliable premedication for gastroscopy

Glasgow Royal Infirmary

DAVID C MILN

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

SIR,—Professor Browne is to be congratulated on his comprehensive paper of Jan 18 He states, "we now have all the essential facts bearing on the ætiology of eclampsia" I would venture to disagree with this, because he fails to give a satisfactory explanation of the cause of the basic pathological feature of pre-eclampsia—namely, placental ischæmia

Professor Browne attempts to explain the cause of placental ischæmia as being overdistension of the uterus in twin pregnancy, and stretching against powerful resistance in primigravidæ, but toxæmia can arise early in pregnancy before there is any overdistension, or before undue stretching of the uterine muscle has occurred Moreover, hypoplasia of the vascular system cannot be the explanation, because toxæmia can be severe in "grand" multiparæ Chronic hypertension, causing diminished placental blood-flow, is also not a satisfactory explanation, for toxæmia can occur in non-hypertensive patients In addition, Professor Browne has explained hypersensitivity of the vascular system as being due to increased chorionic gonadotrophin, but he goes on to admit that this sensitivity of the vascular system, which plays a part in the ætiology of toxæmia, is acquired "from whatever cause in pregnancy" Dornhurst and Young[1] found in guineapigs and rabbits that injections of *l*-adrenaline and *l*-noradrenaline caused a reduction in the maternal placental circulation—a reduction shown by Browne and Veale[2] to exist in cases of pre-eclampsia hypertension in the human Further, they believe that this reduction is not due to the uterine contractions

In another part of his discourse Professor Browne discusses the role of diet in causing toxæmia and in the end could offer no better explanation than increased output of corticotrophin—a fact for which, when discussing toxæmia in diabetic pregnancies, he says there is no evidence

In this department work has been going on for some years in an attempt to identify the pressor factor in the blood of toxæmia patients Some evidence has been collected that the pressor factor may be noradrenaline[3] It seems that there has been a concentration of research on the adrenal cortex, overlooking possible trigger-factor in the adrenal medulla

The outstanding feature of pre-eclampsia is generalised vasoconstriction—particularly in the liver, uterus, placenta, and kidneys Grayson and Johnson,[4] using rats and rabbits, found that "intravenous or subcutaneous noradrenaline frequently produced a diminution in liver blood flow, the local action overriding the reflex dilator action of the raised blood pressure", and that "the local action of noradrenaline on the liver vessels was constrictor" Inadequate intake of protein may lead to diminution in the amount of methionine from the liver necessary to methylate noradrenaline to adrenaline Hence, the original fault may be inadequate protein, a factor which would be present throughout pregnancy, and indeed it would seem that pre-eclampsia is a disease very often built up over a considerable time in pregnancy, and very often controlled by high-protein diet, especially in its early stages. Sims[5] states, "the raised excretion of methionine and choline characteristic of the pregnant state is detectable by the end of the first trimester ... with the methionine there is a falling off in the last trimester probably due to some degree of methionine depletion of the maternal organism at this time."

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[1] The Un. of Birmingham Hosps Annual Cancer Report, 1957, vol 3, Breast

[2] Goligher J C, Thornton H L Lancet, 1951, ii, 652.

[1] Dornhurst A. C., Young I M J Physiol 1952, 118, 282

[2] Brown J C McC., Veale, N J Obstet Gynæc, Brit Emp 1953, 60, 142.

[3] Lennon G G Gardiner, J Path. (in the press)

[4] Grayson, J., Johnson, D H J Physiol 1953, 120, 73

Noradrenaline can raise both systolic and diastolic blood-pressure and can produce a complete arrest of renal blood-flow. Our evidence that the pressor factor is noradrenaline in the blood of the toxæmic woman has been deduced by chromatogram extraction, by biological assay in rats, and by the neutralising of the pressor factor by dibenylene. I would suggest that increased circulation of noradrenaline in the pregnant toxæmic woman is a sufficient explanation of vascular spasm leading to so many of the pathological findings in pre-eclampsia and eclampsia, and especially to the reduction in placental blood-flow and placental ischæmia.

Professor Browne has stressed the clinical similarity of Cushing's syndrome and pregnancy toxæmia. But I believe that there is a closer clinical similarity in the effects of phæochromocytoma and toxæmia. Gemmell[6] has referred to this.

Other work in this department confirms the rise of blood-pressure in the third stage of labour and afterwards in many normal cases. The peak occurs about half an hour after the birth of the child.[7]

I hope that these remarks do not in any way detract from the most excellent paper of Professor Browne and that they merely help to show that "all the essential facts" bearing on the ætiology of this distressing subject have not yet been elucidated.

Department of Obstetrics
and Gynæcology,
University of Bristol

G. GORDON LENNON

TRICHOMONAS VAGINALIS

SIR,—I had hoped for many more comments on this subject, especially concerning those most distressing and difficult cases—the recurrences.

The success of any treatment administered by the patient is prejudiced by a lack of cooperation from a class of patient who expect immediate relief, if not cure.

In treating vaginal discharges, relief from irritation and soreness is so paramount a feature that any treatment which fails in this is often discarded by the patient. A second essential is that the preparation must be æsthetically acceptable to both female and male if necessary. Finally and naturally, the preparation must be effective, and if it has a wide range of activity, such as that claimed for 'Locan' pessaries and cream in the report from Dr. Stewart and his colleagues (Nov. 23), it will be most welcome by clinicians.

My own impression is that, while many preparations fail on one or more of these criteria, locan appears to fulfil all three, and is, therefore, a most valuable addition to our range of local applications.

Croydon

J. C. MILLER

BEE STINGS

SIR,—Reactions of moderate severity to bee stings are not uncommon even among bee-keepers. I myself have kept bees for the past few years and am nearly always stung when I interfere with my bees. On these occasions I usually experience general malaise and fever up to 100°F which may continue for two or three days, together with local pain, swelling, and itching. I have found in my own case and in three other instances that taking 0.5 mg. diphenylpyraline ('Histryl Spansule', Smith, Kline & French) about half an hour before opening the bee-hives prevents all the unpleasant effects. I have also found that as the season progresses I can do without the drug, suggesting that the normal development of immunity is not prevented. Local application of antihistamine cream after being stung is useless in such cases as my own. Some bee-keepers who have had to abandon their occupation on account of reactions to stings could probably have been helped by the simple therapy described.

Bridge, Sussex

F. J. PRIME

TREATMENT OF MYXŒDEMA

SIR,—Dr. Gibson (Feb. 8) has not given the information we hoped for—namely, what method and standards he used for determining his patients' B.M.R.s. Terms such as swinging to the right and left are not very helpful unless we are told above and below what limits the B.M.R. is supposed to be swinging.

Dr. Gibson's views are unorthodox, for most clinicians believe that the B.M.R. is of absolute significance in myxœdema—i.e., the advanced stage of hypothyroidism.

Department of Chemical Pathology,
West London Hospital, London, W.6

I. J. L. GOLDBERG
M. J. SEAMAN

RECTAL RESERPINE

SIR,—The parenteral administration of reserpine may be needed for the emergency treatment of impending hypertensive encephalopathy or cardiac asthma, and for maintenance therapy in mental illness and in children who find difficulty in swallowing tablets. Occasional difficulties with injections have prompted me to prepare and try suppositories of reserpine in coco butter as an alternative.

Each suppository contains 3 mg. reserpine and weighs 2 g. The suppositories were well tolerated, and no sign of rectal irritation was recorded in 31 adult hypertensive patients in the Alexandria University Hospitals.

The effects of these suppositories were compared with those of 3 mg. reserpine, injected intramuscularly in the same patients. Table I shows the hypotensive response to reserpine by both routes, and the efficacy of reserpine suppositories is apparent. A significant hypotensive effect was recorded in 30 out of 31 patients using these suppositories, while the intramuscular injection produced a significant response (a drop of

TABLE I—FALL IN BLOOD-PRESSURE

—	Fall in blood pressure			
	Systolic		Diastolic	
	Intramuscular	Suppository	Intramuscular	Suppository
Whole series				
Mean drop (mm. Hg) in				
1st 6 hours	20	32	12	17
1st 12 hours	21	28	13	16
24 hours	20	26	13	14
Maximum mean drop (mm. Hg)	26	40	15	21
In a single case				
Maximum drop (% of original pressure)	28	39	32	35
Maximum drop (mm. Hg)	65	80	45	45
Maximum mean drop* (mm. Hg) in—				
1st 12 hours	49	55	26	27
24 hours	42	44	25	25

* The mean of the pressure falls recorded in the first 12 hours and in 24 hours was calculated in each case. The largest mean in the whole series is the maximum mean drop.

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[5] Sims, F. H. J. Obstet. Gynæc., Brit. Emp. 1951, 58, 965.
[6] Gemmell, A. A. ibid. 1955, 62, 195.
[7] Edwards, F. M. ibid. (in the press).

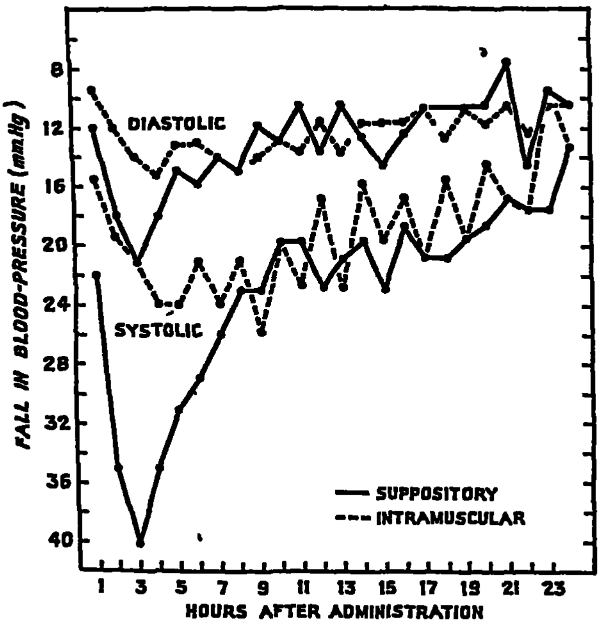
at least 20 mm in systolic pressure and 15 mm in diastolic pressure) in 29 cases

Table II shows that during the first six hours of administration, the number of patients who responded when suppositories were used was almost twice the number responding when the intramuscular route was used The figure represents the average drop of the blood-pressure in the whole series after the administration of 3 mg by each route

TABLE II—NUMBER OF PATIENTS RESPONDING TO 3 MG OF RESERPINE

Time after administration (hr)	Fall in systolic pressure		Fall in diastolic pressure	
	Intra-muscular	Sup-pository	Intra-muscular	Sup-pository
1 hr	9	17	4	9
2 ,,	16	25	10	24
3 ,,	17	28	12	25
4 ,,	21	23	13	20
5 ,,	16	20	12	16
6 ,,	11	20	9	17
7 ,,	18	18	16	12
8 ,,	15	15	12	15
9 ,,	16	17	15	9
10 ,,	16	15	12	12
11 ,,	18	17	16	12
12 ,,	12	19	11	17

Thus, reserpine suppositories have a rapid, sustained and significant hypotensive effect when compared with the intramuscular injections The rapid action is explained by the rich vascular drainage of the rectum, the sustained action is due to the bigger mass of fat in the rectum from which the drug diffuses much more slowly than from muscle tissues Sheppard et al [1] showed that radioactive reserpine disappeared from the organs and the tissues in two hours, while, in contrast, fat tissues still contained a high amount of radioactive material up to six hours later



Average fall in blood-pressure in whole series after reserpine 3 mg

The bradycardic effect of reserpine, administered rectally or intramuscularly, was more or less the same The suppository dose of reserpine is equal to the parenteral dose.

Faculty of Medicine
Alexandria University, Egypt

M H GHANEM

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[1] Sheppard H Lucas R. C., Tsien, W H *Arch int Pharmacodyn.* 1955, 103, 256

SYRINGES CLEAN OR STERILE?

SIR,—I was a little disturbed to see Dr Jackson's reference (Feb 1) to sterilising his syringes in a hot-air oven at 160°C

When testing a large variety of ovens, we found that some were extremely variable when loaded, and this does not seem to be generally appreciated

As an example, an oven which was within ±3°C when empty with the thermometer registering 160°C, gave temperatures varying between 140°C and 188°C, with the thermometer registering 160°C, when three-quarters full with well-spaced syringes in baskets

This means that a fair proportion of these would certainly not have been sterilised, since I believe that the latest work by Dr Darmady shows that a minimum of 160°C is necessary for certain spores

Perhaps Dr Jackson would care to insert a number of thermometers in different places and try to check that he runs the coolest part of his oven right up to temperature, bearing in mind particularly that what is wanted is the temperature inside the barrel of the syringe and not in the air of the oven

Townson & Mercer Ltd,
Croydon

R BARRINGTON BROCK
Director

ATARALGESIA

SIR,—I am grateful to Dr Selwyn Crawford (Dec 14) for raising some points which I did not make clear in my preliminary report (Nov 16)

My primary object has been to devise a method which, especially in disasters and war, will relieve pain, preserve the cooperation of the injured, increase the proportion of "walking wounded", and reduce the quantities of anæsthetics and post-operative medication required The following additional reports of the use of my pethidine-amiphenazole-'Pacatal' (and/or chlorpromazine) combination illustrate some of the possibilities

CASE 1—A policeman was given 3 units by intramuscular injection in the ward, after which, in the theatre, both big-toenails were avulsed and the nailbeds scraped He carried on an animated conversation the while, screwing up his face, but making no attempt to withdraw his legs as each nail was removed He then stepped unaided off the table, and walked five yards to the trolley The sensation, he said, was similar to that of stubbing his toe "but not nearly so bad"

CASE 2—A man of 28 had extensive (25%) acid burns of legs, thighs, genitalia, and lower abdomen He was given 3 units and a full toilet was performed Subsequent dressings were intolerable except under 2 units (A placebo injection did not mislead him)

CASE 3—An Indian woman of 42 received $2^1/_2$ units intramuscularly after which her fractured radius and ulnar bones were reduced while she stood She walked to the X-ray department and returned with her wet films, the position being unsatisfactory, the fracture was manipulated several times more, after which she again acted as her own messenger to and from the X-ray department She seemed "amused about the whole affair"

CASE 4—After $1^1/_2$ units, a boy of 7 climbed out of bed, walked to the theatre, mounted the table, and opened his mouth, from which eleven teeth were extracted He looked like whimpering once, but was distracted Sliding off the table, he announced that three of the pennies presented to him would be spent on sweets, and the remaining eight would be saved up

While working up to the present combination, I conducted 29 surgical cases using pethidine-amiphenazole-chlorpromazine (and/or promethazine) in increasing doses As in Dr Crawford's obstetric cases given pethidine and chlorpromazine, these patients showed "disturbance of mind" (semi-drunken—probably because they had chlorpromazine instead of pacatal) and thus did not attain true ataralgesia, although 12 required no complementary anæsthetic It was to emphasise the retention of mental clarity under the pacatal mixture that I administered 2 units to myself half an hour before reading my paper to the South African Medical Congress last September

The patients for cæsarean sections were given $2^1/_2$ units intramuscularly in the ward one hour preoperatively (no other premedication) The infants were born 79, 105, and 82 minutes later respectively All babies have cried immediately and lustily Relaxation was adequate but not perfect, and bleeding was minimal

It is quite possible that levorphanol will prove as satisfactory as amiphenazole A series is now being investigated for comparison

I agree that the intravenous route may be advantageous at times, particularly in midwifery, but the central effect is greater, and, if cortical depression is apparent, the case must be classed as an ataralgesic failure

Ataralgesia is, by definition, contrary to the type of relaxation produced by muscle relaxants—i e , flaccidity through loss of tone When the relaxation required is really an overcoming of spasm due to pain—as with fractures, dislocations, trismus, or thoracic immobilisation—ataralgesia is usually sufficient in itself It does not, of course, relax abdominal muscles, but factors such as laxity of muscles, or even shock may facilitate abdominal surgery, and in the event of mass casualties much pain-free repair could be undertaken, albeit under less than ideal conditions

In my paper, no claim was made that intra-abdominal operation (apart from the cæsarean sections) was performed under successful ataralgesia Nevertheless, five such operations were performed without complementary anæsthesia A transdiaphragmatic nephrectomy for a stab wound required assisted respiration only A Wertheim's hysterectomy, an operation for intestinal obstruction, excision of a large chorion epithelioma, and a 210-minute gastrectomy were all performed, increasing the central effect and using intermittent minimal doses of gallamine Intubation is quite possible without a hypnotic (cf conditions under the " lytic cocktail ")

I must repeat that my report was a preliminary one and as such left much unsaid It has been clear from these investigations, however, that there are many sidelines and other applications of ataralgesia, as well as deliberately modified forms of it in surgery, medicine, dental and veterinary work, and, in particular, obstetrics

Durban, South Africa J T HAYWARD-BUTT

SIR,—Under the guidance of Dr Hayward-Butt, I have been using " ataralgesia " in obstetrics The following interim report of ten normal deliveries may be of interest

A combination of pethidine, amiphenazole, and ' Pacatal ', using $2^{1}/_{2}$ units, was given when the patient's cervix was approximately four-fifths dilated The average period between its administration and the delivery of infant was 55 minutes In no case was the newborn infant distressed The average period between the infant's birth and its first cry was $1^{1}/_{2}$ minutes All mothers reported marked relief of pain and only one was uncooperative after the injection Intravaginal manipulations caused no pain or complaint There were no cases of postpartum hæmorrhage and, apart from acute mastitis in one case, no postpartum complications

Two forceps deliveries were also performed with satisfactory results

CASE 1 —Mrs A , aged 17, 42 weeks pregnant, went into labour at 9 A M At 1 P M the cervix was fully effaced and dilated, the vertex presenting in transverse diameter After $^{3}/_{4}$ hour, no advance was noted and pethidine-amiphenazole-pacatal ($2^{1}/_{2}$ units) was given by intramuscular injection 12 minutes later, forceps was applied and a live female infant weighing 8 lb was extracted The placenta was expressed 5 minutes later, there was no abnormal blood-loss The application of forceps was easy , the patient experienced no pain and was cooperative at all times

Before extraction of the head, episiotomy was undertaken and, as the patient felt some pain, 1% lignocaine was given in the line of the incision

CASE 2 —Mrs B , aged 38, 4-gravida, went into labour at 10 P.M Vaginal examination at 8 A.M next day showed the cervix to be fully dilated with the vertex presenting in transverse diameter As the patient was distressed, forceps delivery was decided on and pethidine-amiphenazole-pacatal was given at 8 A.M At 8 30 A.M a live male infant was extracted with forceps He cried immediately, the placenta was expressed after 7 minutes, and there was no postpartum hæmorrhage.

Manual removal of the placenta was performed in another patient She was cooperative and felt no pain

The results in this small series suggest that, when given with amiphenazole, large doses of pethidine (up to 300 mg half an hour before delivery of the infant) could safely be used in obstetrics

Durban, South Africa C J GOOSEN

IDIOPATHIC STEATORRHŒA WITH HYPOPROTEINÆMIA

SIR,—Dr Forshaw has reported a case of idiopathic steatorrhœa with severe hypoproteinæmia [1] We should like to report 2 similar cases and make some comments on the subject

CASE 1 —A man, aged 56, had noticed swelling of the ankles and legs for three weeks The swelling had varied somewhat and tended to increase after heavy work He had been given digitalis, but as this drug had no effect on the swelling he was sent to hospital He had moderate œdema of the ankles and legs The serum-protein was 4 4 g (albumin 1 5, globulin 2 9), serum-calcium 7 6 mg , and serum-iron 62 µg per 100 ml , hæmoglobin 73%, and erythrocyte-count 3 8 million per c mm He was first treated with a high-protein diet for six weeks, without appreciable effect on the serum-protein When the diagnosis was established he also got a low-fat, low-cereal diet, and in another six weeks the serum-protein increased from 4 8 to 6 5 g per 100 ml and the œdema disappeared He has since had the same diet, and serum-protein and calcium values have been normal The only abnormal finding in this patient during the past year has been an intermittent anæmia with depression of serum-iron, which has responded well to iron by mouth

CASE 2 —A man, aged 39, had persistent swelling of the ankles and legs and periods of loose motions His doctor prescribed a diet consisting mostly of fish, and with hardly any milk With this diet his bowel symptoms disappeared except for an occasional loose motion now and then Three months later he got tetany and was admitted to this hospital The investigations showed serum-protein 4 9 g (albumin 2 0, globulin 2 9), serum-calcium 6 1 mg , and serum-iron 26 µg per 100 ml , hæmoglobin 77%, and erythrocyte-count 4 1 million per c mm The signs of tetany subsided spontaneously shortly after admission and have not appeared since A few weeks later he reported some sensations of the same type, but no tetany developed The treatment was ordinary hospital diet during the first month, and serum-protein and calcium increased somewhat but did not reach normal values, the œdema, however, disappeared, within the first weeks When the diagnosis of idiopathic steathorrœa was established, a high-protein, low-fat, low-cereal diet was given and a control investigation two months later revealed normal protein (7 4 g per 100 ml) and calcium (9 7 mg) He has remained on this diet and kept well except for a tendency to anæmia and low serum-iron, but the response to oral iron has been good

During the past fifteen months we have observed 2 other patients with idiopathic steatorrhœa

CASE 3 —A man, aged 65, had for many years had intermittent bowel symptoms His symptoms increased, with anorexia and loss of weight He had no œdema, but the serum-protein was 5 0 g per 100 ml He is keeping well on the diet described above and the serum-protein has become normal

CASE 4 —A man, aged 52, had for some months had anorexia, loss of weight, and bowel symptoms A year previously he had had the same symptoms for some weeks, but recovered spontaneously He was very ill on admission with a serum-protein of 4 1 g per 100 ml Despite all therapy he died six weeks later

We are not convinced that hypoproteinæmia is as unusual in idiopathic steatorrhœa as Dr Forshaw states

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[1] Forshaw, J W B Lancet, 1957, ii, 720

The protein metabolism in this disease has not attracted much attention until recent years, and we believe there is increasing evidence that the albumin, at least, is often decreased to some extent. Adlersberg et al [2] report serum-protein determinations in 67 patients with idiopathic steatorrhœa, and in 19% of these the total protein content was less than 5 g per 100 ml In 60 of these patients the serum-albumin was determined, in 52% it was less than 3 5 g per 100 ml In 16 patients (24%) œdema was present at the time of admission

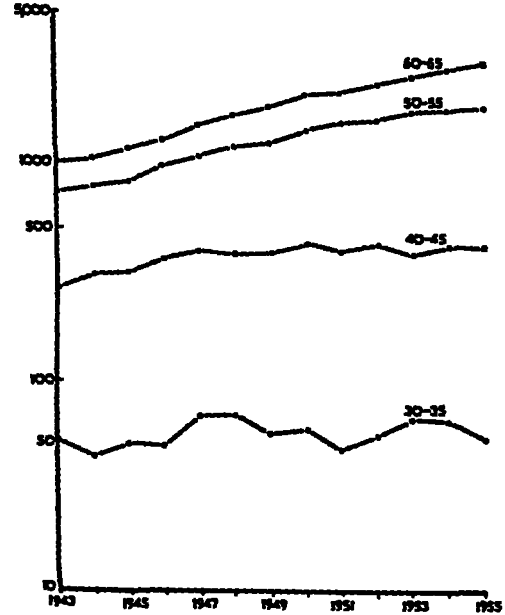
Medical Department, County Hospital, Falköping, Sweden.
HOLGER WAHLUND
NILS D WESTAD

ANOTHER CANCER FALLACY

SIR,—Your lucid annotation on the fallacy of the decreasing lung-cancer death-rate with extreme age appears to condone the almost identical fallacy of the latent period of the effects of the cigarette It states that "those now 65 have been more exposed to this hazard" It might be preferable to state that they "are being more exposed".

Although analogies from mice and mule-spinners, and the assumptions implicit in the remarkable strategy of contemporary experimental research, may lead to an expectation of a latency of several decades, the available data on man do not allow the inference that the memory of the lung for tobacco is more than a few years

The apparent latent period between the imports of tobacco and the consequent deaths is exactly what would be expected if an irritant acting only over quite short periods were to be the daily indulgence of a population whose resistance to neoplasia was steadily reduced with advancing age, and whose smoking habits were largely determined in youth.



Deaths from lung cancer in males in England and Wales in 1943-55.

This fallacy is of some importance not only in relation to the relevance of research on animals not liable to spontaneous bronchial neoplasms, but also in that many middle-aged smokers, fearing that their lungs will always carry the scars and memories of past decades, see no reason to protect their bronchi from further irritation

As the liability to death from lung cancer doubles every 3 to 4 years between the ages of 30 and 70, the basic rate being 10-20 times higher in the heavy smoker than in the non-smoker,[1] the present virtual restriction of preventive measures to schoolchildren cannot be expected to have much influence on the death-rate until almost a million persons have died from this disease in Great Britain alone. Some idea of the appalling risks to which the ageing smoker is increasingly exposed may be conveyed from the calculation that a free issue of cigarettes to old-age pensioners would save the Government the greater part of the cost of the tobacco

The accompanying figure gives some idea of the present pattern of increase in this disease

Department of Social Medicine, Medical School, Birmingham
J H EDWARDS

INFLUENZAL ENCEPHALITIS

SIR,—The letter of Dr McGill and Dr Goodbody last week, recording cases of acute hæmorrhagic leucoencephalitis and referring to those reported by Dr Dubowitz (Jan 18), prompts us to make it known that three fatal cases of leucoencephalitis have come to necropsy in this area during the past few weeks The naked-eye appearances of the brain were closely similar to those depicted by McGill and Goodbody

In addition we are aware of other cases in which the patients have apparently recovered completely, and at least one other where the issue is still in doubt We have not observed a clear association in these cases with an immediately preceding attack of influenza Nevertheless in view of the foregoing reports we think it desirable to publicise the fact that cases of hæmorrhagic leucoencephalitis are occurring in widely separated parts of the country.

It is hoped that every opportunity will be taken by all who observe such cases to search for an infecting virus both during life and at necropsy

Pathology Department, University of Glasgow
JOHN H STEPHENS
D F CAPPELL

INFORMAL ADMISSION OF MENTAL DEFECTIVES

SIR,—I have read with interest Dr Heaton-Ward's letter (Feb 8)

While Memorandum H.M (58)5 recommends the informal admission of suitable cases to mental-deficiency hospitals and the review of the patients already detained, it does not repeal the present Mental Deficiency Acts

With regard to the review of patients already in hospital, the medical superintendent is asked to submit to the Board of Control the names of patients who might suitably remain on an informal basis without certification and legal detention.

It appears, therefore, that we can go ahead and take action to implement the recommendations of the recent Royal Commission as far as these concern bringing mental-deficiency hospitals more into line with ordinary hospitals, and use certification and detention only where absolutely necessary for the protection of the patient or the community

In the case of the majority of our patients the decision will be relatively easy, but there is bound to be a hard core of patients where one would hesitate to dispense with legal control These cases present great difficulty in any case, but personally I cannot agree that the memorandum will make our task harder Indeed I regard this circular as being the most encouraging document the mental-deficiency service has received since the report of the first Royal Commission of 1908

Bromham Hospital, nr Bedford.
T A. DANBY
Medical Superintendent.

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[2] Adlersberg D, Wang, C. I., Bossak, E. T., in Adlersberg, D The Malabsorption Syndrome p 32 New York, 1957

[1] Edwards, J H Brit J prev soc. Med. 1957, 11, 10

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—Mr Moloney in his excellent paper of Feb. 8 implies inadvertently that the recurrence-rate of 14·3% for simple herniotomy (1940–45) in adult males which I recorded[1] referred to an operation which also included a repair of the fascia transversalis at the internal ring. This was not so. Later in the same article I reported a small series of 9 adult cases in all of whom success was achieved by excision of the sac combined with suture of the ring. This was first done by Marcy of Boston (1871) and since 1951 I have continued to use it successfully in those patients who at operation are found to have entirely congenital sacs with narrow necks.

London, W.1 CAMERON MACLEOD

SIR,—I was much interested in Mr Moloney's article. The results are excellent by any standard, and must be a strong argument in favour of nylon as the most useful suture material. May I add one criticism and one comment.

The results appear to have been ascertained by a postal questionnaire. Many patients are unaware of a recurrence (or even of a primary hernia) until it strangulates. Furthermore, only 76% of the patients replied to the questionnaire, and there is no reference to the seeking of information from the general practitioners of the missing 24%. The figures for the recurrence-rate cannot, therefore, be anything but very approximate, and cannot be compared satisfactorily with the results of reviews obtained by actual examinations of the patients. Is there no hope of obtaining the results of examinations of these patients?

In the teaching hospitals of the Liverpool region all inguinal-hernia repairs in adult males are registered, and reviewed after one and three years. Between 1951 and 1954, in 450 patients whose hernias were repaired with nylon, 17 developed a sinus failing to heal within two months, 19 further operations were effected to remove pieces of nylon, and 9 cases had a discharge for a year or more—1 for five years. I have not the figures available (as I write) to determine whether the nylon in the affected cases had been monofilament or braided, but I will check this; I think monofilament nylon was used in most of the cases. Admittedly, the cases I quote were dealt with in the main by registrars, whose results one would not expect to equal the personal series of an experienced surgeon. Nevertheless, it cannot yet be accepted that nylon is free from serious disadvantages as a suture material in the repair of inguinal herniæ.

St. Helens, Lancs. A. J. MARSDEN

TECHNIQUE OF INTRA-ARTICULAR INJECTION

SIR,—Mr Grant Waugh's letter of Dec. 28 is indeed timely. Much relief can be given to patients by the use of intra-articular injections of hydrocortone, but there is no need for this to be associated with any pain or discomfort.

The knee-joint is treated most frequently and I feel that more consideration should be paid to the injection route in an attempt to avoid pain during the procedure. The usual techniques of injecting on either side of the patellar tendon are to be avoided because the needle does not necessarily enter the joint space or even pierce the synovial membrane as the whole of the apparent space between the femoral and tibial condyles is, in fact, occupied by the alar fat pad and if the hydrocortone is deposited in this structure it causes severe pain.

The method adopted in our practice is to displace the patella laterally with the knee fully extended and insert a short small-bore needle into the tense capsule at the "superolateral corner" of the patella. This manœuvre creates an artificial space which is reached by piercing merely skin, subcutaneous tissue, capsule, and synovial membrane without having to traverse any other tissues. This procedure is completely painless and does not require the use of a local anæsthetic. It is also of great value in aspirating the knee-joint.

Durban, South Africa CYRIL KAPLAN

ASSISTED RESPIRATION DURING GALLAMINE ANÆSTHESIA

SIR,—In a number of patients who receive gallamine ('Flaxedil') in the course of anæsthesia induction, the initial period of apnœa is followed by tracheal tug. This may persist for a varying length of time while spontaneous respiration is becoming established again.

During the initial phase of tracheal tug, respiration is so depressed that there is little or no movement of the rebreathing bag, to guide the anæsthetist in the timing of assisted respiration.

However, if a finger of one hand is placed over the patient's larynx whilst the other hand grasps the rebreathing bag it is now possible to synchronise assisted respiration with the early efforts of the patient—i.e., with the tracheal tug.

Later, as respiratory efforts increase, it will be found that this method will give better timing of assisted respiration than judgment based upon the fluctuations of the rebreathing bag alone, since the anæsthetist's own reaction time will be shortened.

St. Giles Hospital,
London, S.E.5 P. A. P. POMPA

INFANTILE GASTROENTERITIS

SIR,—I was interested to read the article by Dr Brown and Dr Bailey on the treatment of infantile gastroenteritis.[1] In my experience cortisone is often a life-saving drug.

In the tropics gastroenteritis is usually seen in a very advanced stage. The infants are often practically moribund—dehydrated, cyanosed, and with dry staring eyes. It has always been difficult to get this type of patient, with a sluggish peripheral circulation, to absorb and retain fluids, and in those cases in which rehydration was established dehydration rapidly recurred. But since we have adopted the following routine for the treatment of infantile gastroenteritis we have been able to overcome this difficulty and reduce the mortality very considerably.

(1) Intramuscular drip infusion, using hyaluronidase, of this solution:

Sodium	25 mEq	Lactate	23 mEq
Potassium	20 mEq	Phosphate	3 mEq
Magnesium	3 mEq	Water	1 litre
Chloride	22 mEq		

200 ml. is given into each leg simultaneously and repeated 4-hourly if necessary.

(2) Cortisone intramuscularly *5 mg.* 4-hourly.

(3) Antibiotics: if the child is vomiting severely, *50 mg.* oxytetracycline is given 8-hourly intramuscularly, but the usual routine has been to give streptomycin 0·25 g. 6-hourly by mouth, together with half a tablet of phthalylsulphathiazole.

(4) Water by mouth, until vomiting stops, then half-strength milk feeds.

Cortisone seems to assist in the rehydration of patients with peripheral vascular failure, and prevents fluid loss once rehydration has been established. It is possible to withdraw the cortisone suddenly about the fourth day, once the diarrhœa has stopped, without ill effects.

Unfortunately it has not been possible to establish scientific figures because staff is short and the pathological department is already overworked. I would add that there is tremendous overcrowding in the wards, isolation is impossible, and very often two infants have to be nursed in the cot. Cross-infection is practically never seen and no precautions are taken regarding disposal of napkins or feeding, since there is a great shortage of nurses I feel, however, that cortisone should be given an adequate trial in a gastrointestinal unit

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[1] *Lancet*, 1955, ii, 106.

[1] Brown, E. H., Bailey, E. H. *Lancet*, 1957, i, 1218.

General Hospital,
Taiping, Perak, Malaya.

B E BARSBY

AMAUROSIS FUGAX

SIR,—Sir Philip Livingston's very interesting article [1] brings to mind a striking case

A woman, aged about 50, had a large painful ulcer on the right side of her neck, following X-ray and radium treatment for a supposedly malignant tumour The ulcer was larger than a man's palm, with a hard sloughing base Its upper edge was 1–2 cm below the mandible Biopsy showed no malignant cells

I began treatment with injections of her own blood (40 ml, not altered by citrate) under the edges of the ulcer—a treatment which I had found successful in previous cases when healing was slow After two injections the pain was less At the third treatment, when about 5 ml of blood had been injected under the superior edge, she suddenly became blind in the right eye, her right eyeball was protruded, and the pupil dilated and insensitive to light The left eye was unchanged I stopped the injection, sight returned to the right eye, and was normal in 4–5 min

War-time conditions prevented me from investigating this case further I have seen no similar event in over fifty years of practice, and I cannot explain it except as a reflex response Stimulation of the carotid body was unlikely for anatomical reasons

Budapest.

ANDREW MAKAI

THE LIONEL WHITBY MEMORIAL FUND

SIR,—We should appreciate your assistance in calling attention to a fund being raised by the Master and Fellows of Downing College, Cambridge, in memory of their late Master, Sir Lionel Whitby, regius professor of physic in the University

The Lionel Whitby Memorial Fund was established at the suggestion of the Downing College Association and an Appeal has been sent out to its members It is proposed to use the fund to found Whitby Memorial Scholarships in the college, an object which, it is felt, would have met with his warm approval

As an undergraduate of the college he was a Scholar, and later became successively Honorary Fellow, Professorial Fellow, and finally Master, and the college was one of the chief interests of his life It has been suggested to the Master and Fellows that among his wide circle of friends in the medical world there may be many, in addition to members of the college, who would like to contribute to this Memorial Fund

The Master and Fellows would very much welcome such contributions, as the resources of the college are among the most limited of those of the Cambridge colleges Although the college now spends from its general resources nearly £4000 annually on scholarships and exhibitions, only about £1000 of this is provided from specific endowments It was the heavy demand thus made on the general endowments of the college, together with a wish to keep alive the memory of Whitby in the minds of future generations of undergraduates, which led the Association to allocate the present fund to the foundation of scholarships bearing his name

Contributions should be sent to the Bursar, Downing College, Cambridge, and if so desired, may be made by seven-year covenant, forms for which will be supplied on request

W K C GUTHRIE
GORDON GORDON-TAYLOR
HAROLD BOLDERO
E C DODDS
R W SCARFF
JOHN KIRK

Parliament

Children of Broken Marriages

ON some of their most important recommendations the members of the Royal Commission on Marriage and Divorce were divided Not unnaturally these recommendations led to controversy and discussion among the public But the group of recommendations urging that the children of broken marriages should be offered more protection and security was readily accepted on all sides, and on Feb 7 Mr ARTHUR MOYLE introduced, as a private member, the Matrimonial Proceedings (Children) Bill which will give legislative shape to the Commission's suggestions

In his opening speech Mr Moyle said that each year the parents of over 20,000 children were parted in divorce, which meant that 1 child in 20 was deprived of a normal home That was not the kind of basis on which children could build well for their future lives One main provision of his Bill was to ensure that no final decree, either in divorce or judicial separation, could be made final until the court was satisfied that as far as practicable satisfactory arrangements had been made for the future of the children A second important provision was to set up a court welfare service to assist the judge in reaching decisions about the custody of the children

Mr DAVID RENTON, joint under-secretary of State for the Home Department, in welcoming the Bill on behalf of the Government, said that the lives and happiness of a considerable number of children were affected by the disputes of their parents and it was right that the courts should pay regard to their welfare If the Bill became law he was sure that those who administered the law would welcome the new powers and responsibilities which it would give them

Shrimps, Prawns, and Pickled Onions

On Feb 10 Mr FREDERICK WILLEY prayed against the proposed amendment to the Food Hygiene Regulations (S I 1957, no 2157) which, subject to safeguards, would except shrimps, prawns, and pickled onions from the embargo on the processing of food in the homes of outworkers Most of the debate rightly centred round the shrimps and prawns, for unlike the onions, they are peeled in the workers' homes after and not before they are boiled, and no form of sterilisation, however informal, comes between them and the consumer Many members were clearly uneasy about their preparation in the home Time must elapse between preparation and sale, children must be cared for, babies must be changed, and constant supervision by the manufacturer or the local authority is impossible

Mr RICHARD THOMPSON, parliamentary secretary to the Ministry of Health, said that, though there was no reason why food could not be prepared in domestic premises in as clean a way as in a food factory, absence of supervision could admittedly permit lower standards than people nowadays expected for the preparation of food But the present regulations offered some safeguards They laid down that outworkers' premises must be registered with the local authorities Outworkers must also observe the ordinary provisions laid down in the food and hygiene regulations to ensure the personal cleanliness of the worker and the protection of the food from contamination. (These standards do not, however, seem too exigent, for in response to questions Mr Thompson agreed that an "adequate supply of hot water" did not require a water heater, but could be met by water boiled in a kettle and that "reasonably accessible" could mean a basin in the next room) It was, he pointed out, difficult to find workers to undertake these particular jobs, and the Minister had accepted that it would not be practicable to change arrangements in these two industries without severe dislocation But the Minister also accepted the desirability of replacing outworking as soon as possible by methods which would ensure adequate supervision of peeling There was provision to review the working of the regulations in two years' time The motion was withdrawn

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[1] *Lancet*, 1957, ii, 1129

QUESTION TIME

New Drugs

Mrs **SLATER** asked the Home Secretary what precautions were taken to protect the public from the marketing of new drugs which might be likely to cause harm to the public if used without proper safeguards —Mr **DAVID RENTON** replied There are special provisions for the control of drugs coming within the scope of the Dangerous Drugs Act or the Therapeutic Substances Act Before placing new substances on the market manufacturers take every precaution, if necessary by laboratory tests and clinical trials, to ensure that they are not harmful Where it is found, either before a drug has been marketed, or afterwards, that it may have harmful effects, the Poisons Board are asked to consider whether it should be controlled as a poison

Mrs **SLATER** Is not the Minister aware that there is vast and growing concern at the amount of drugs which are now being put on the open market and which can thus be bought quite freely? Is he aware that there have been several cases of people who have suffered very badly—some have landed in mental homes and some have even died—as a result of the free sale of these drugs? Is not it time that these drugs were referred to the Poisons Board before being put on the open market?—Mr **RENTON** I am not sure whether the hon Lady is referring to what are known as new drugs If she is, then that is a matter which should be put to the Minister of Health Of course, a great many of the well-known and established substances are perfectly harmless when taken in moderate quantities and can become dangerous only when taken in excess There would be no point in making such substances into poisons from the technical point of view In any event, it is for the Poisons Board to use its initiative in this matter

Suicide and Attempted Suicide

Mr **KENNETH ROBINSON** asked the Home Secretary if he would introduce legislation to amend the law relating to suicide and attempted suicide.—Mr **R A BUTLER** replied I am not satisfied that any change in the law is desirable Mr **ROBINSON** Is the Home Secretary aware of the considerable and growing opinion in the medical and legal professions, and among the general public, that the legal view of suicide is more and more at odds with society? Has not the time come to take this matter completely outside the category of criminal offences?—Mr **BUTLER** The present concept of suicide as a crime has its roots in religious belief Although it is true that there is greater sympathy and understanding for suicides and would-be suicides, there is no evidence in my possession that the alteration of the basic concept would be universally acceptable to public opinion I do not underestimate the point that the hon Gentleman has put to me, I am simply trying to assess the present position

Certification

Dr **D JOHNSON** asked the Minister of Health whether the statement of Dr W S Maclay, a principal medical officer of his department, made in Toronto on Jan 22 was made with his authority, and how far the conclusion embodied in it was based on facts collated within his department —Mr **DEREK WALKER-SMITH** replied I understand that this statement was made in the course of a long and comprehensive address to a meeting of Canadian psychiatrists on British mental health services It was intended only as a humorous reference to some medical certificates which, as evidence of unsound mind, had been rejected by the Board of Control over a number of years Dr **JOHNSON** Does not the Minister appreciate that Dr Maclay, in his statement in Toronto, a report of which stated

"… that doctors' reasons for certifying patients as being of unsound mind 'often makes one wonder whether it is the doctor o the patient who should be certified'"

was, in fact, drawing attention in, perhaps, rather colourful fashion to the same problem of improper certification, and will he not ask Dr Maclay to amplify his statement on his return to this country?—Mr **WALKER-SMITH** I will certainly discuss it with Dr Maclay, but I do not think it would be very rewarding to pursue seriously with him something that was meant in lighter vein to sugar the pill of the solid and serious argument to which he was addressing himself on this occasion

Mr **H H DODDS** But how can the Minister justify saying that it was said in fun when thousands of people in this country are being certified by one doctor without any special knowledge of mental troubles? When one of his chief representatives goes abroad and makes a statement like that, how can he say he was just having fun? If the Minister is making fun of it, does he not think of the thousands of people who are having to bear this stigma—and their children and grand children? Surely, it is not a thing to make fun about —Mr **WALKER-SMITH** As I am sure the hon Gentleman knows, it is not an uncommon practice among practised and persuasive speakers to try to introduce a little lighter note into a serious argument, and it has never been held that that convicts them of any improper levity in their approach to a serious subject

Social Services

In 1938 about 34% of Central Government current expenditure was on social services, in 1956–57 the figure was 37% Current expenditure by all public authorities on social services was about 10% of the national income in 1938 and 15% in 1956–57

Windscale Accident and London

Radioactive iodine was detectable in the atmosphere over London after the Windscale accident on Oct 11, 12 and 13, 1957, but in very much smaller amounts than in the Windscale area By Oct 14 the level had fallen below the limits of detection

Obituary

GWYNNE EVAN OWEN WILLIAMS

M D, M S Lond, F R C S

As we announced last week Mr Gwynne Williams, consulting surgeon to University College Hospital, London, died on Feb 3

He was born at Luton in 1881 and went to Bedford Grammar School and later to University College, London He qualified from University College Hospital in 1903 As a student and resident he played rugby for the hospital, and he was treasurer and president of the medical society In 1905 he took the M D Lond, and the following year the M S and F R C S For a time he held a registrarship at the Seamen's Hospital, Greenwich, but in 1910 he was appointed surgical registrar at U C H Four years later he was appointed surgeon and he held this post until he retired in 1946 He was also on the staffs of the Royal Northern Hospital and the Cheyne Hospital for Children

During the late war he was in charge of the casualty-clearing services of the hospital, and he lived there during all the air-raids He gave the hospital notable service as chairman of the medical committee and as dean from 1935 to 1943 A M H G, whom he succeeded in the deanship, writes

My association with Bill, as he was always called at U C H, began when we were students He was slightly my junior, but we were in residence together and when we both decided to set up in practice, we took rooms together, which we shared for nearly ten years We were also closely associated at the medical school It is difficult for a colleague to assess the professional eminence of another colleague in a different branch of medicine, as one sees little of that side of his work In fact I don't remember ever having seen Bill operate, but I have been told by surgical colleagues how much they respected his opinion on difficult cases As a teacher he was superb Conscientious to a degree and tireless, he got the very best out of his students and though he made their path hard, they loved him for it

He was of a retiring disposition and to a stranger often appeared to be somewhat fierce He certainly did not suffer fools gladly, and could at times be rude, but beneath this somewhat forbidding exterior he could be kindness itself, and his many friends will never forget the help he gave them

To Gwynne Williams' work as a surgeon one of his colleagues, who was once one of his students, pays the following tribute

His surgery was developed in the days before anæsthetics were as safe or as smooth as they are today, when speed mattered, and the apparently effortless way in which he performed a wide variety of surgical operations was remarkable He practised before specialisation in surgery was common but had a particular interest in the treatment of fractures He was a pioneer in introducing to this country the ambulatory treatment of some leg fractures, and was one of the first to use the Smith-Petersen nail in fractures of the femoral neck His shyness did not allow him to speak easily at professional meetings, but in smaller gatherings there was much to learn from his very wide and acutely remembered experience

His was the sort of personality that throve, developed, and made an impact on the life of the hospital Operating, teaching, in the wards most days and often at night for emergencies, he was there and seen to be there He drove himself hard in his younger days and expected and got hard service from his juniors Conscientious himself, he did not hesitate to castigate sloth, but he was generous to anyone who tried, and his example led many to try hard In his later years, some of his apparent fierceness—and it was only apparent—mellowed, though his energy diminished not at all and he continued to get through an immense amount of work His old students will long recount to each other tales of his mannerisms, his laughter, his abruptness, his energy Bill was a very real man, and, now in their middle age, those former students will realise again how much they owe to him, from whom they learned their art and in whom they saw an example of the duty the doctor owes his patients and his work

Mr Williams leaves a widow and three sons, two of whom are doctors

A memorial service will be held in St Pancras Church, Euston Road, N W 1, at noon on Monday, Feb 17

Mr KENNETH BOWES

A G M, who was one of his students, writes

The most obvious of Mr Bowes' many outstanding qualities was his kindliness He had the gift of always saying the right thing at the right moment, so that everyone felt at ease in his presence His exceptional intellectual power and honesty gave him brilliant judgment, and, coupled with a delightful sense of humour, made him an inspiring teacher He never taught at the bedside The reason for this, he explained, was that on one occasion he was describing what it felt like to produce a baby when the patient looked up and said "Sez you" This so shamed him that thereafter he met his class in the sideward, where he taught us a great deal of midwifery and gynæcology Among his most popular stories were those of "patients who have caught me out", and the favourite of all was of "the patient who caught me out twice"

Diary of the Week

FEB 16 TO 22

Monday, 17th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Mr Murray Falconer Temporal Lobe Epilepsy

HUNTERIAN SOCIETY
8 30 P M (Mansion House, E C.4) Dr Macdonald Critchley Animal Communication

Tuesday, 18th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C.1) Dr Paul Fourman Potassium Depletion

ST MARY S HOSPITAL MEDICAL SCHOOL, W 2
5 P.M Dr J M Holmes Breech Presentation and Delivery

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Mr A T Gray Ointment Bases

UNIVERSITY OF ST ANDREWS, Queen's College, Dundee
5 P.M Dr R P Cook Investigation of the Lipids

Wednesday, 19th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street W 1
5 P M *Comparative Medicine* Dr W F H Jarrett, Dr W I M McIntyre, Dr W Mulligan Dr F Jennings, Dr G M Urquhart, Dr J K Walley, Dr O D Standen Recent Progress in Treatment and Prevention of Helminth Infections
8 15 P M *General Practice* Dr R. M McGregor, Dr J G Ollerenshaw Emergencies in General Practice

POSTGRADUATE MEDICAL SCHOOL
2 P M Dr Rosemary Biggs Blood Coagulation Factors in Theory and Practice

INSTITUTE OF DERMATOLOGY
5 30 P M. Dr Henry Haber Basal Cell Epitheliomata

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr E H Hudson Use of Cortisone in Pulmonary Tuberculosis

WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P M (Star and Garter Hotel, Putney Bridge, S W 15) Dr R D Teare Role of the Pathologist in the Investigation of Crime

BIRMINGHAM MEDICAL INSTITUTE Highfield Road Edgbaston
8 P M *Psychiatry* Dr J L Clegg, Dr R J Stanley Report of the Royal Commission on the Law Relating to Mental Health

NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY, 64, St James s Street, Nottingham
8 30 P M Prof R J V Pulvertaft Cinemicrography in Diseases of the Blood and Lymph Nodes

Thursday, 20th

UNIVERSITY COLLEGE LONDON, Gower Street, W C 1
5 P M Dr F H C Crick The Nucleic Acids—Function (Second of three lectures)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Prof P L Krohn Processes of Ageing in the Reproductive System

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W 1
8 P M Dr G M Ardran, Dr F H Kemp Radiological Investigation of Infant Feeding

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place W 1
7 30 P M Prof B S Platt Malnutrition and Pathogenesis of Zymotic Diseases

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P M Dr G N C Crawford Growth of Muscle

MANCHESTER MEDICAL SOCIETY
8 P.M (Staff House, University of Manchester) *Anæsthetics* Dr H J Brennan Terminal Apnoea

Friday, 21st

ROYAL SOCIETY OF MEDICINE
5 P.M *Epidemiology and Preventive Medicine* Dr E J L Lowbury, Dr J B Selkon, Dr H Williams Smith Epidemiological Risks of Antibiotics
8 15 P M *Radiology* Dr Gordon Osborne Dr J N Pattinson Benign Lesions of the Pyloric Antrum Simulating Carcinoma. Dr Benjamin Green Dr R A Kemp Harper Radiological Diagnosis of Malignant Gastric Ulcer Dr L S Carstairs Headache and Gastric Emptying Time

KING S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S E.5
4 30 P M Prof Robert McWhirter Recent Advances in Breast Cancer (Dorothy Platt lecture)

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr I H Griffiths Incontinence of Urine
4 P M Dr A G MacGregor Idiopathic Hæmochromatosis

INSTITUTE OF LARYNGOLOGY AND OTOLOGY 330, Gray s Inn Road W C 1
3 30 P M Mr Wallace Black Chronic Ulcers in the Mouth and Pharynx
5.30 P M Dr T V L Crichlow Radiology of the Temporal Bone

FACULTY OF RADIOLOGISTS
4 15 P M (Royal College of Surgeons Lincoln s Inn Fields, W C.2) Dr George Ansell Radiological Findings in Patients Treated with Cortisone and A C T H

Notes and News

CONGRESSIONAL COMMITTEE ON FALLOUT

In May and June last year, the special subcommittee on radiation of the United States Congress joint committee on atomic energy heard evidence on the nature of radioactive fallout and its effects on man, and the proceedings have been published verbatim with many appendices, including the Medical Research Council report *The Hazards to Man of Nuclear and Allied Radiations* and many other reports, symposia, and statements This abundant source of material for reference is published by the United States Government Printing Office in Washington, in two parts, with a total of 2055 pages There is no index

WHAT TO DO WITH SPUTUM

In the prevention of spread of tuberculosis, safe disposal of the sputum of patients is extremely important Those who have to care for tuberculous patients, whether in institutions or at home, will welcome a pamphlet[1] published by the Joint Tuberculosis Council It describes the types of container and handkerchief (and handkerchief pocket) that are suitable, and the ways of destroying or effectively disinfecting them, 'Polythene' flasks, in which the sputum can be treated with a hypochlorite solution, are recommended The pamphlet also gives advice to those who have to collect sputum containers, and the addresses of the manufacturers of all the equipment discussed

University of Glasgow

On Jan 25 the degree of M D was conferred on A R W Climie (in absentia)

Royal College of Physicians of London

Dr Charles Newman will give an "Unofficial FitzPatrick lecture" at the college on Friday, Feb 28, to a meeting of members

The meeting is open only to members, who may bring their wives to the lecture and to the sherry party to be held immediately after Tickets are needed for the sherry party and can be had from the secretary of the college, Pall Mall East, S W 1, not later than Feb 17

Royal College of Surgeons of England

The honorary fellowship has been conferred on Prof Warren H Cole (Chicago), Prof Clarence Crafoord (Stockholm), Prof F L-P de G d'Allaines (Paris), Prof C F W Illingworth (Glasgow), Dr Charles W Mayo (Minnesota), and Prof Herbert Olivecrona (Stockholm)

Royal College of Physicians of Edinburgh

At a meeting of college on Feb 4 with Dr A Rae Gilchrist, the president, in the chair, the following were elected to the membership

M M El-Nahas, Wilhelm Horowitz S N Basu Subramoney Nadarajah, Gopala Kuppuswamy, R N Dutta F E Abdel-Gadir, C P Lowther, J N Wattie, A M I Wasfi, W J Gomes G R Sparrow, M W Partington Ivan Hyde, Harry Coll, M N Khan R A Papworth, Ramachandra Pararajasegaram J F Moodie N J W Royston, Shih Chang Hu A L Hilton Shishu Pal Ram, G B Jain, Kamla Gupta, B W Cromie B K Ahuja, R A Harkness

James Yearsley Lecture

Mr Francis McGuckin will give this lecture at the Royal Society of Medicine, 1, Wimpole Street, London, W 1, on Friday, March 7, at 5 15 P.M His subject will be recent developments in tympanoplastic surgery

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold a public hearing on Thursday, Feb 20, at 11 15 A M, at 10, Carlton House Terrace, London, S W 1 Representatives of the General Practice Reform Association have been invited to attend

Rockefeller Foundation

During the last quarter of 1957 the Foundation distributed over $19 million Grants for medical education and public health amounted to some $3 million, and for biological and medical research to $2½ million

Noxious Effects of Low-level Radiation

A symposium on this subject will be held in Lausanne from March 27 to 29 The speakers will include Dr W G Marley, Dr W M Court Brown, and Dr N Stewart Further particulars may be had from the secretary, Schweizerische Akademie der Medizinischen Wissenschaften, Petersplatz 13, Basle, Switzerland

Merseyside Medical Art Society

This society, which was founded last year, is holding an inaugural dinner in Liverpool on April 2, to be followed by an exhibition which will be open to the public

The president is Prof B G Maegraith, and membership is open to any doctor resident on Merseyside and environs Further particulars may be had from the secretary, Dr D B Mossman, pathology department, Warrington General Hospital

French Scientific Films

The films to be shown at the Institut Français, Queensberry Place, London, S W 7, on Wednesday, Feb 26, at 8 30 P M, will include films on the role of the larynx in voice production, circulation in the pulmonary alveoli, and the physical and social reablement of accident cases Tickets may be had from the scientific office, French Embassy, 22, Wilton Crescent, S W 1

An Eli Lilly medical research fellowship ($3600 per annum) is open to South African doctors who wish to do research in the United States Further details can be had from Dr H Shapiro, P O Box 1010, Johannesburg The closing date for applications is April 30

On Tuesday, Feb 25, at 5 30 P M, at the Fountain Hospital, Tooting Grove, London, S W 17, Dr L Fisch will give a lecture on the differential diagnosis of deafness and mental deficiency

Nursing and Midwifery is the latest booklet in the Central Youth Employment Executive's Choice of Careers series It may be obtained from H M Stationery Office and costs 1*s* 9*d* A companion booklet, *Nursing for Men*, will be published later this year

The second edition of the *UFAW Handbook on the Care and Management of Laboratory Animals* can now be had from the Universities Federation for Animal Welfare, 7a, Lamb's Conduit Passage, London, W C 1 (pp 920 70*s*)

Appointments

BOWIE A T, M B Glasg assistant M O H, assistant school M O, Dumfriesshire

BRIDGE A J, M R C S, F D S consultant dental surgeon Guy's Hospital London

SHORT, I A, M B Glasg M R C P, F R F P S part time consultant physician, Western Infirmary, Glasgow

SYKES BLANCHE, M R C S, D P H assistant M O (maternal and child welfare), Northumberland

Manchester Regional Hospital Board

FERGUSON, R S, M D Glasg, D P M consultant psychiatrist and medical superintendent, Lancaster Moor Hospital

FIRTH JOSEPH M B Leeds M R C O G part time consultant obstetrician and gynæcologist, Bolton and district hospitals

GOLDBERG I J L B SC South Africa M R C S assistant pathologist Oldham and district hospitals

WILLIAMS R G, M B Lond assistant chest physician, Wigan and Leigh and Wrightington hospitals

Births, Marriages, and Deaths

BIRTHS

GRIFFITHS —On Jan 31 to Barbara and Glyn Griffiths M B of 170, East Dulwich Grove, S E 22—a son Charles William brother for Mary Anne and Caroline

DEATHS

BINGHAM —On Feb 4 Raymond Glendon Bingham M R C S, formerly of Garden House, Limes Avenue Alfreton

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[1] Joint Tuberculosis Council Report of the Public Health Committee on Collection and Sterilisation of Tuberculous Sputum in Hospital and at Home Copies obtainable without charge and post free from Dr R L Midgley Hawkmoor Chest Hospital, Bovey Tracey, Devon

The Lancet · Saturday 22 February 1958

SPINAL ANÆSTHESIA

THE PRESENT POSITION*

NORMAN C LAKE
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HONORARY CONSULTING SURGEON, CHARING CROSS HOSPITAL, LONDON

IN the seventy years since Corning of New York first used spinal anæsthesia in a patient, the method has had its periods of waxing and waning popularity In some centres it has always been, and remains, relatively acceptable, while in others it is never used or even considered There can be no doubt, however, that in this country spinal anæsthesia is now rather out of favour, this is confirmed by the diminished sales of such anæsthetics which the manufacturers report. I think the reasons for this are fairly obvious, in the forefront is the widespread attention which has been drawn to certain particularly tragic results in the way of permanent paraplegias, but there have been other factors too There is, for instance, the comparatively recent introduction of the paralysant, the hypotensive, and the hypothermic drugs as adjuvants to general anæsthetics, nor must it be overlooked that the development of slow operative methods by surgeons makes spinal anæsthesia, with its limited duration, less suitable The continuous or fractional techniques by which it is sought to circumvent this shortcoming are of necessity associated with additional risks which I do not feel are justified Finally, few anæsthetists, and still fewer surgeons, seem sufficiently interested in the possibilities of this form of anæsthesia to acquire the special technique, or to adopt the psychological atmosphere essential to success

The conclusions here reached are based on a personal experience of well over 2000 administrations The great majority of these have been high spinals for upper abdominal operations, given by a method published nearly twenty years ago (Lake 1938), it is particularly with these that I deal now

Risks

In considering the risks of any form of anæsthesia, a distinction must be made between what may be called the accidents of administration, or errors of technique, and the inherent hazards of the method concerned For instance, there are reports of cases where with local anæsthesia the injection of a wrong-strength solution caused death, where a rectal injection of the wrong anæsthetic material led to a fatal gangrenous proctitis, where raw chloroform was introduced into the trachea owing to a mistaken connection of tubes, where intra-arterial injections of anæsthetics caused gangrene of a limb, and so on Such accidents are paralleled in spinal anæsthesia by the cases where solutions containing adrenaline or of high alcohol content were injected intrathecally, in a recent case it was accepted in Court that phenol had got into the ampoules, and there are proved cases where microbial infection has been introduced

These, however, are all errors of technique and are not valid as evidence against any particular form of anæsthesia After excluding them we are left with the basic mortality and morbidity, in which general and spinal anæsthesia should be comparable Unfortunately, it is not easy to collect large numbers of strictly comparable cases, nevertheless it is at least a pointer that the Registrar General's report for the years 1950–52 (chosen because they cover the period before the recent slump in spinal anæsthesia) gives the rather startling figure of 1874 deaths attributed to anæsthetics, in 1799 of these the anæsthetic responsible was stated Of this number, 1770 were general and 29 local or spinal anæsthetics It is surprising, and chastening, to find that in no less than 208 cases thiopentone was the sole anæsthetic used, so that even so simple a form of general anæsthesia is associated with a considerable risk to life Although these figures give no grounds for complacency, they do not help our comparison because we do not know the relative numbers of general and spinal anæsthetics given Failing incontrovertible statistical demonstration of the risk to life, one must fall back on personal experience It may seem audacious to say that in the series of spinal anæsthetics mentioned above there have been no deaths attributable to the anæsthetic, for the very next case may upset these figures I cannot, however, in the face of this experience, bring myself to believe that the risk to life is greater than that of general anæsthesia, if indeed it is as great

Morbidity

Of course mortality is not the only criterion by which anæsthesia should be judged, there is also the question of subsequent morbidity, temporary or permanent On the credit side for general anæsthesia, permanent morbidity is rare, though there are reports of lung damage from inspired material, of toxic effects on the liver and kidneys, and of cerebral damage associated with cardiac arrest (a condition I have not come across with spinal anæsthesia) Some temporary morbidity following general anæsthesia is, however, not uncommon, the laryngotracheitis, which often makes the patients complain that it is worse than the operation itself, may last for a considerable period, temporary pulmonary collapse with the possibility of an added infection may cause anxiety, venous thrombosis and cellulitis from extravenous injection or leakage can be both troublesome and protracted, and there are other less important sequelæ

On the other hand the morbidity associated with spinal anæsthesia must be fully recognised Pulmonary complications, though not common, are by no means unknown The headache that follows spinal anæsthesia is, however, the commonest aftermath. it rarely lasts for more than a day or two, and with proper posturing and suitable drug control both its incidence and its severity are largely overcome. Very rarely indeed is it more persistent, one patient in this series told me that he was not entirely free from a tendency to headache until three months after the operation, but this is exceptional External-rectus palsy of more than twenty-four hours' duration has been noted in 6 cases In only 2 of these did it last longer than a week, and even then only when the patient was tired, in both it cleared completely in two to three months With high spinal anæsthesia, urinary difficulty is probably no commoner than with general anæsthesia, but with low spinals temporary trouble is occasionally seen

The most serious complication is of course paraplegia or a more localised motor paralysis So tragic are the results of a paraplegia that, though it must be an extremely rare sequel, it weights the scales unduly against spinal anæsthesia The numerical incidence remains unknown, there has been no case of paraplegia in the whole of this series

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* Paper read at Charing Cross Hospital to the surgical section of the Royal Society of Medicine

One patient who was given a spinal anæsthetic many years ago complains of a feeling of weakness in the legs, but, as she has no neurological signs and is a neurotic who has had a total colectomy for ulcerative colitis, it seems unlikely that the weakness is related to the anæsthetic In a patient who had had a gastrectomy, some wasting and paralysis of certain shoulder muscles noted after the operation were attributed by a neurologist to the spinal anæsthetic, but subsequently the man's doctor came across some old notes made before the operation in which these signs had already been described

When dealing with a lesion of unknown ætiology, neurologists undoubtedly tend to attribute it to any spinal anæsthetic which may have been given I cannot speak from personal experience of paraplegia due to spinal anæsthesia, but many cases have been recorded in which the evidence seems incontrovertible If we exclude those in which accidentally the wrong, or a contaminated fluid has been injected, there remain others where the technique was apparently perfect Three main hypotheses are advanced to account for the condition: (1) that it is a direct toxic effect of the drug upon the neurones of the cord (Lundy et al 1933), (2) that it is due to an adhesive arachnoiditis set up by the irritative properties of the anæsthetic, or (3) that it is a virus infection

The first of these can probably be dismissed, since there is a good deal of clinical evidence that the anæsthetic acts on the fine nerve-roots and not on the cord itself The experimental evidence of a direct effect on the cord was obtained from work on animals that have little cerebrospinal fluid (C S F) around the cord, using much stronger concentrations of drugs than are ever given clinically It is well known that it is hard to avoid paraplegia in certain animals even with simple lumbar puncture The fact that some of the reported cases arose together (i e , in the same operating session, or in a very limited period of time) has suggested a virus infection No causative virus has been démonstrated, but it is worthy of note that as far back as 1909 Sir Victor Horsley reported 21 cases in which there was paraplegia of spontaneous onset, due to what was then called meningitis serosa circumscripta but is almost certainly the same condition as has been found after spinal anæsthesia and called adhesive arachnoiditis Horsley propounded a virus origin because one of his cases followed an attack of herpes zoster

The explanation most commonly advanced nowadays is that the adhesive arachnoiditis is due to the direct irritative effect of the injection, and it is alleged that this is commoner after cinchocaine ('Nupercaine') than other anæsthetic drugs, possibly because of its pH or hypotonicity or hypertonicity (Thorsen 1947) The difficulty in accepting this suggestion is that if the solutions are indeed so irritant it is surprising that only a very minute percentage of patients show any signs of meningism, and with meningeal irritation one would expect an increased C.S F pressure, whereas it is well established that after spinal anæsthesia the C S F pressure is low for a time—indeed the headache is attributed to this, and is certainly made worse by anything (e g , lumbar puncture or drugs) which lowers it still more

Horsley (1909) showed that the condition, whatever the cause, can arise spontaneously

> Many years ago I failed to achieve a satisfactory spinal tap although I felt the needle penetrate the dura only a drop or two of fluid could be obtained—a so-called "dry tap" Spinal anæsthesia was therefore abandoned, and the patient was given a general anæsthetic under which he succumbed At necropsy the reason for the failure was shown to be an unsuspected meningitis serosa circumscripta

And so, unhappily, we are compelled to leave unsolved the question of paraplegia I feel, however, that in some of the cases the cord itself may have been punctured, either because its termination was unusually low, as it invariably is in children and patients with spina bifida (which may be occult), or because of a miscount of the lumbar spinal processes, the topography of which may at times be quite difficult to determine in obese patients For this reason, although most of the injections in this series have been given between the 2nd and 3rd lumbar spines I now advise that punctures should not be made higher than the 3rd or 4th lumbar spine While recognising how tragic paraplegia is let us not lose all sense of proportion, after all, patients die under general anæsthesia, but that is no reason for abandoning it

Advantages

What then is to be said to the credit of spinal anæsthesia? By means of a single injection we achieve not only anæsthesia but at the same time relaxation and hypotension Having spent many years trying to combat the widely accepted idea that the controlled hypotension of spinal anæsthesia was harmful, I now find it difficult to enthuse over the various methods by which hypotension is achieved supplementary to general anæsthesia In some clinics the patient has actually been bled at the beginning of an operation and the stored blood returned at the end, surely it is better to store the blood in the patient's own vascular system

The relaxation achieved in spinal anæsthesia is, in my opinion, more satisfactory than that which the relaxant drugs give It is complete and not subject to variation, while at the same time the muscles outside the zone of action retain their activity and tone This later point is important as Beecher and Todd (1955) showed In a large series of comparable cases collected from various clinics, they found that relaxants considerably increased the overall anæsthetic mortality, and they suggested reasons for this, one of which was the fact that all voluntary muscles are relaxed regardless of the limits of the operative zone As all surgeons know, modern anæsthetic techniques combined with relaxants are apt to produce some increased bleeding unless hypotensive drugs are used as well, at times this can be more than a nuisance A further advantage of spinal anæsthesia that the abdominal operator appreciates is that the bowel remains actively contracted, though this does not in any way interfere with the stitching when making an anastomosis

There remains to be considered the psychological aspect, and this concerns not only the patient but also the surgeon and anæsthetist, for successful spinal anæsthesia demands correct handling of the patient's fears and misgivings and a strict mental discipline for all those in the operating-theatre For some nervous and unstable people this form of anæsthesia is obviously unsuitable, it would be cruel to expect them to submit But, for the majority,

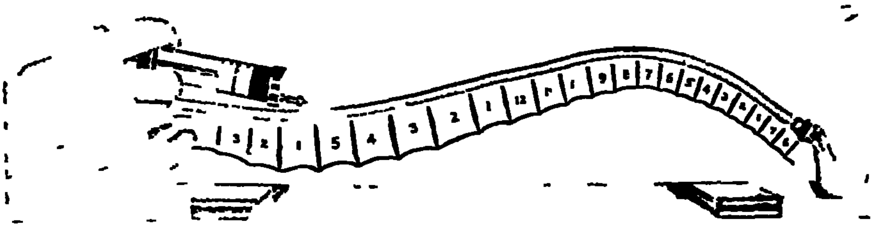

Fig 1—General arrangement of apparatus and injection of hypobaric coloured solution. To demonstrate effect more clearly only small amount of solution is used.

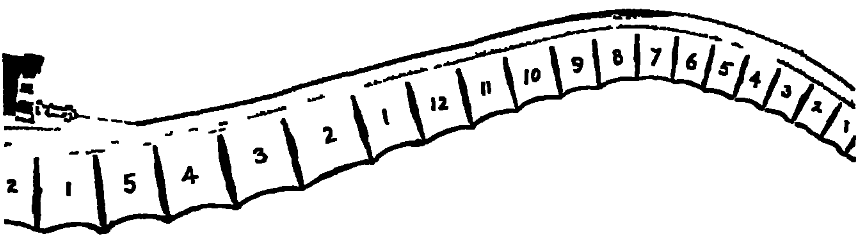

Fig 2—When injection is made very slowly, solution travels up as discrete stream and collects in vicinity of highest point. Only about 2 ml. had been injected when photograph was taken.

once they are convinced by the start of the operation that they will feel nothing, the method has great merit. I have known many patients fall asleep during an operation under the influence of the small preoperative injection probably enhanced by the fall of blood-pressure.

Method

Since it is conceivable that some of the drawbacks mentioned may be related to the particular method used, a very brief description is necessary of the technique in this series for high anæsthesia—i.e., up to the 2nd thoracic level.

In the majority of cases the solution has been either 1/1500 or 1/1000 spinal cinchocaine, the latter strength giving a little longer anæsthesia (up to about one and a half hours in the upper abdomen) but the technique being otherwise the same. Simple premedication is given with morphine and atropine about twenty minutes and ephedrine gr. $^3/_4$ ten minutes before the lumbar puncture; scopolamine is apt to make older patients uncooperative. The patient lies face downwards on the table, and by a suitable arrangement of pillows the 7th dorsal spinous process is brought to the highest point of the curve of the spine. The injection is made in the midline at the spinous interspace 3/4 lumbar. With a fine hypodermic needle the skin and interspinous ligament are anæsthetised with the same solution (the ampoules contain 20 ml., so there is plenty to spare). For many reasons which there is no need to elaborate I think this preliminary injection is essential. The fine short-bevel spinal needle (a lateral aperture is an inessential refinement) is introduced vertically to the surface slowly and deliberately until the dura is felt to be penetrated and C.S.F. starts to flow. The needle is now advanced a very slight amount more to make sure that its orifice is completely within the dura, and if there is a lateral aperture this is turned cephalad. The flow of C.S.F. should be slow but nevertheless quite certain, in any case of doubt the patient may be asked to cough or the jugular vein may be compressed in the neck. After a few drops have thus escaped, a syringe containing the warmed cinchocaine is attached carefully without disturbing the needle and the injection made very slowly indeed. The amount varies with the size of the patient and the nature of the operation, a gastrectomy in a large man will need about 9.5–10 ml., while for a small woman 7 ml. will be sufficient. About two minutes should be taken over the injection of these quantities; when it is complete the needle remains in situ for a further half minute before withdrawal. The patient is kept in the same position for ten minutes and is then turned gently on to his back and the table given a 4–5° head-down tilt. The operation can be immediately started with confidence; for the surgeon's assurance a towel clip may be surreptitiously applied to the skin of the upper abdomen, and at the same time he may note that the underlying muscles are flaccid by observing the ineffectual attempts of the patient to cough when requested. In particular the patient's faith should not be undermined by asking him if he can feel, for it must be realised that he remains just as conscious of his anæsthetised abdominal wall as the patient after amputation does of his phantom limb.

Such an administration gives anæsthesia which extends from about T2 to L3, and for the upper abdomen lasts for one and a quarter to one and a half hours. It does not, however, block the vagal or phrenic sensory supply. The vagus subserves the special sense of nausea, rather than true pain, which tends to be aroused when traction is applied to the stomach. For the most part the nausea can be abolished by a circumœsophageal injection of anæsthetic when the abdomen is opened. Phrenic pain, referred to the left shoulder, is likely to be caused only if there is incautious swabbing under the dome of the diaphragm; suction should be used here and the patient warned that he may feel a little aching over the shoulder. I have never found this to be a serious drawback.

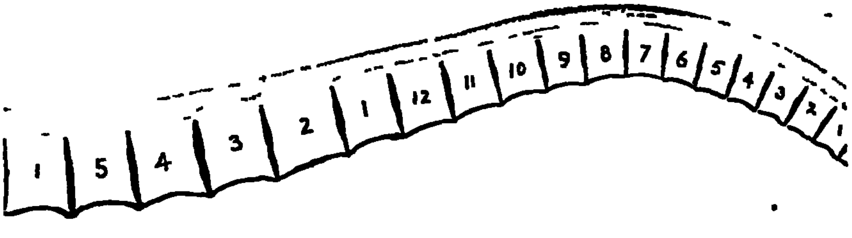

Fig 3—Even after several minutes injected solution diffuses but slowly into the surrounding fluid.

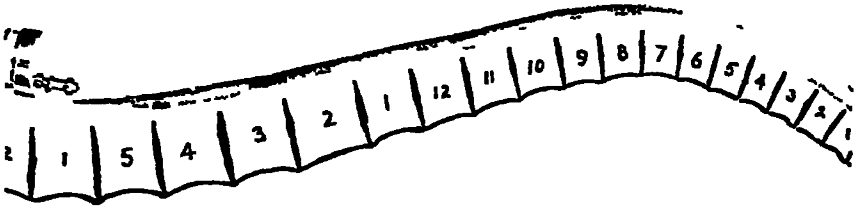

Fig 4—When injection is made rapidly admixture is immediate and localising effect is largely lost. Much more fluid had been injected than in previous illustrations, yet concentration at highest point is less.

Demonstration

The distribution of the solution in the theca by this method can be most convincingly demonstrated by the use of a polyethylene tube bent to the usual curvature of the spine (fig 1) The tube, like the dura, is closed at its lower end, while at the head end is a small rubber balloon to represent the capacity of the cranial cisterns The tube is filled with water, the solution injected is water that has been rendered slightly lighter (hypobaric) by the addition of a very small amount of alcohol and coloured with a suitable dye (eosin) If this solution is injected slowly at a level corresponding to L3/4 it will be seen to travel up as a localised stream on the dorsal aspect of the tube to a point somewhat beyond the highest point of the curve (fig 2) In the demonstration the amount injected is much less (2 to 3 ml) than the volume of anæsthetic used in practice For many minutes this stream remains discrete, it diffuses only slowly into the surrounding fluid (fig 3) If, on the other hand, the solution be injected rapidly, turbulence at the needle-point produces immediate mixing with the water in the tube, with great dilution of the solution and loss of localisation (fig 4)

In the actual spinal theca the presence of the cord, the nerve-roots, and the dentate ligaments obviously tends to divide the space into anterior and posterior compartments and to enhance this localising effect The fact that the stream remains discrete is very important to this particular technique, because the anæsthetic solution used is in great dilution (1/1500) to start with, and if immediately further diluted by admixture with a large amount of C S F it will of necessity lose a lot of its anæsthetic power Some of the few failures reported may well be due to this effect

The chief physical forces concerned are two displacement and gravity The capacity of the spinal theca to accommodate any extra fluid is very slight, and, as the lower end is a cul-de-sac, when an injection is made fluid must be displaced towards the head, where it is accommodated in the intracranial cisterns Gravitational forces are responsible for determining that it is the lighter injected fluid which shall be displaced rather than the C S F, and that it shall travel up the posterior compartment of the theca as a discrete stream Later diffusion, pulsation, and other minor forces play a small part in the further distribution of the fluid

Indications

Spinal anæsthesia is not suitable for the extremely ill or shocked patient, or, in my opinion, for the very old patient with a rigid vascular system or for patients with severe hypertension, none of these stand the fall of blood-pressure well It is clearly not available for long operations lasting several hours, but there is nevertheless a wide range of operations in which its ability to afford the surgeon anæsthesia, relaxation, and hypotension by a single injection makes it an ideal method

I should like, therefore, to recommend a renewed interest in spinal anæsthesia for suitable cases, like all other anæsthetic techniques it has its risks, but it also has great merits which are plain to see unless one is unduly biased

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THE ROLE OF RESPIRATORY INSUFFICIENCY IN THE MORTALITY OF SEVERE HEAD INJURIES

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RESPIRATORY insufficiency exists when gas exchange between the lungs and the blood falls below that between the tissues and the blood Thanks to the work of Lassen (1953) and his colleagues in Copenhagen, and to other pioneers, the management of severe respiratory insufficiency in poliomyelitis complicated by bulbar palsy is now well established, and the mortality has been lowered to 20%

We believe that there is a similar problem of respiratory insufficiency in the unconscious patient with a severe head injury, and that anoxia is the main cause of death in patients who survive the accident but die at a later stage

It is true that the onset of pulmonary infections or œdema has been noted as contributing to death after a few days, and that, in the past, tracheotomy has been advocated as a method of dealing with chest complications at a late stage, but, in our opinion, respiratory insufficiency exists from the time of the accident in the unconscious patient, and, if it is tackled early, pulmonary complications will be avoided and the mortality notably reduced

Many authorities have assumed that the condition following a severe head injury depends probably on a combination of vascular upset, physiological neuronal injury, and organic neuronal injury, and that it may be rapidly changed by the development of such complications as cerebral œdema We believe that, whatever the actual picture (unless the patient is killed outright), provided the brain can be given an adequate supply of oxygen from the beginning and the chest complications dealt with early, many patients can overcome the initial injury and local primary œdema following lacerations and contusions and will survive to make a good physical and mental recovery In other words, if the brain-stem can still function, the essential centres can keep life going, the onset of a secondary anoxic œdema can be prevented, and even severe intracerebral damage can be overcome, and damaged neurones, if receiving an adequate oxygen supply, can in many cases recover normal function

The combination of coma, hyperpyrexia, and decerebrate rigidity, which precedes death in these cases of severe injury, is similar to that following asphyxia without any associated trauma, and we believe that cerebral œdema is essentially caused by anoxia, secondary to respiratory difficulties The ultimate success or degree of permanent damage, in our view, depends on the degree and duration of the associated anoxia Nerve centres have already been damaged by the intracranial lesion, the cerebral circulation and respiration are impaired, and events, unless rapidly checked, move quickly so that one form of anoxia is superimposed on another, exerting their combined action on already susceptible nervous tissue

During the past few years we have noted the following significant factors

At necropsy many patients dying from severe head injuries at an early stage after the accident have vomit and blood-clot in the bronchi and bronchioles, and early changes in the alveoli are present histologically, even where clinically there were no chest signs of any significance

Radiographs of the chest may show partial or total collapse of a lung at an early stage.

Subendocardial hæmorrhages are commonly present in the heart over the Bundle of His, suggesting a significant degree of anoxia

When patients with head injuries complicated by brain-stem injury or compression have been taken to the operating-theatre, have been intubated, have had their lungs sucked out, and have been given enough oxygen for the purpose of operation, there has been a dramatic improvement in the pulse-rate, respiratory rate, colour, and general condition, but this has not been maintained once the tube has been taken out.

Physiology of Respiration and Respiratory Failure

The rates of replacement of pulmonary capillary blood and alveolar air are determined respectively by the body's metabolic demand for cardiac output and by the respiratory-control mechanisms which are also geared largely to the level of body metabolism Metabolism exerts its control mainly by carbon-dioxide production and the associated levels of CO_2 tension and pH

Alveolar ventilation is usually so precisely regulated that alveolar (and arterial) CO_2 tension seldom deviates from 38±3 mm Hg (sea-level value) and the arterial blood pH is 7 40±0 05 When control centres are depressed by sedative drugs, anæsthesia, or disease such as bulbar poliomyelitis, the fine control of ventilation is lost and respiratory acidosis evolves As anoxia develops, the oxygen chemoreceptors in carotid and aortic bodies take over the respiratory drive In sudden respiratory failure, metabolic and circulatory events happen with extreme rapidity, death ensuing within as little time as three minutes, because there are essentially no stores of oxygen in the body Faced with developing anoxia and asphyxial acidosis, the heart responds first with increased force of contraction, probably because of adrenal discharges , then, as myocardial anoxia ensues, the cardiac output and blood-pressure rapidly fail and death follows unless drastic means are at hand to restore oxygen and contractibility to the heart

In severe head injuries the same picture presents In many cases severe damage to the pons, medulla, and hypothalamic areas are produced by distortion and impaction of the brain as the result of linear movement, rotation, acceleration, and contrecoup damage within the skull, thus seriously depressing the respiratory-centre control by direct injury or by interference with the vascular supply of the essential centres In addition, owing to damage to the vagal nuclei, as happens also in bulbar poliomyelitis, the control of the larynx and pharynx becomes disorganised in many cases, thus allowing exudation and secretion to pour down into the bronchial tree

Mechanics of Breathing

The passive components of mechanical behaviour of the respiratory pump are resistance and compliance

Resistance consists essentially in pressure-loss due to the flow of gas through the tubular respiratory passages In severe head injuries the patient is deeply unconscious and is often carried face upwards , this causes mechanical obstruction of the airway He is often, in addition, bleeding from the nose or nasopharyngeal area, and may have cerebrospinal fluid pouring into the pharyngeal area from a fracture involving the anterior fossa of the skull Stimulation of the vomiting centre by the injury or by early anoxia often causes vomiting Solid vomit (if the patient has recently had a meal), acid gastric contents, blood (both fluid and clotted), and cerebrospinal fluid may thus easily find their way into the bronchial tree, particularly as laryngeal and pharyngeal control is disorganised and the cough reflex often abolished. This will lead to further increase in resistance by blocking of the trachea or bronchi

Compliance is an expression of quasi-static relationship pertaining particularly to elastic tissues and surface tension of respiratory surfaces The dimensions of compliance are change of lung volume per unit change of " static " pressure difference between the inner and outer surface of the lungs Blockage of the bronchial tree, as described, with the onset of partial or total collapse, will make the lung less compliant and thus less distensible In addition, if the bronchioles are obstructed, a negative pressure is produced in the alveoli, causing exudate of fluid and pulmonary œdema, and thus again lowering the distensibility of the lungs Interference with the hypothalamic area by injury may also, by an alteration of sympathetic and parasympathetic balance, produce a so-called pulmonary œdema Compliance is also affected by the irritation produced by inhaled blood, acid stomach contents, solid vomit, and cerebrospinal fluid, which rapidly produce changes in the alveolar epithelium itself The walls of the alveoli become swollen and œdematous and are rapidly covered by a layer of fibrinous exudate These local factors in the chest interfere with the Hering-Breuer reflex leading to further inadequate respiratory effort

If the local factors are not dealt with quickly, secondary lung involvement will follow, with infection and death rapidly supervening The combined central and local factors rapidly produce severe anoxia, and unless this is immediately tackled, cerebral tissue is permanently damaged, with secondary cerebral œdema due to anoxia and stagnation, and the patient's chance of recovery is hindered or completely lost

Treatment

We believe that if adequate oxygenation can be maintained by dealing with these local and central factors, even the most severely injured patients may survive, and since we have carried out treatment along these lines our mortality has been lowered from 90% to 40% In our opinion, it can be lowered even further by improvement in technique

The whole aim of treatment is to regard these respiratory factors as vital in immediate treatment of a severe head injury to prevent anoxia and lung damage There are two main needs, besides any neurosurgical intervention (1) the patient must have full oxygenation, and (2) the chest must be kept clear of infection to allow oxygenation to take place The two obvious means at our disposal—namely, oxygen administration and antibiotic cover—were proved inadequate by the number of patients who died of anoxia and severe chest infection Many of these had marked changes in the lungs Clot and vomit lay in the bronchi and bronchioles and, at necropsy, obvious changes in the alveoli had already taken place

Next, we placed our patients in the " tonsil position " or prone, and sucked out the pharynx, but this by itself was unsatisfactory We then considered the use of endotracheal tubes As a short-term emergency measure this was quite satisfactory, provided the airway could be kept clear by suction, but there is a danger of increasing resistance by using a catheter for suction through an endotracheal tube A cuffed tube prevents the drainage of exudate from the disorganised larynx or pharynx As a long-term measure there are certain disadvantages in the use of endotracheal tubes, for they are liable to cause laryngeal œdema and actual necrosis if retained longer than twenty-four hours, and in addition a dead column of air persists in the bronchial tree

The Question of Tracheotomy

We were led now to consider tracheotomy as a more effective means of maintaining an airway, providing ease of suction, and doing away with a dead column of air which, because of inadequate respiratory excursion, prevents oxygenation of the lungs

To begin with, we limited ourselves to patients who had obvious clinical signs and symptoms of fluid in the chest which could not be cleared by suction via the mouth and larynx by means of a catheter and who showed signs of anoxia The results were not wholly satisfactory The fluid was easily and frequently sucked out and some patients improved Many, however, still died from chest infections and anoxia, and we felt that it was too late to wait until clinical signs appeared in the chest before doing tracheotomy We therefore decided to widen our indications Tracheotomy was carried out on all patients who, clinically, had signs of fluid in the chest, no matter how small an amount we imagined the fluid to be, and on all patients who had a serious nasal or postnasal hæmorrhage or cerebrospinal leak Antibiotic cover, of course, was continued No resort was made to any postnasal packing, which we had tried previously and abandoned because of the onset of meningitis in one or two cases It was found that suction with a cuffed tracheotomy tube was quite sufficient to maintain a clear airway—the blood-loss in these cases being dealt with by blood replacement

In these two groups of unconscious patients there were, therefore, to our minds, definite indications for immediate tracheotomy, whether or not neurosurgical intervention was contemplated , in fact we are unwilling to consider their treatment complete without its being performed as soon as possible

A third group of patients still gave us concern these were the ones who did not fit into the pattern of those already described, who were unconscious but had no apparent nasopharyngeal blood or cerebrospinal-fluid, leaks into the chest, whose colour was apparently normal, and in whom the chest showed no physical signs for twenty-four hours or so Necropsy indicated that, in many cases, they too had serious chest complications from the start, the aspirated material consisting of acid stomach contents or solid vomit, presumably aspirated before arrival at the centre In some cases where the physical signs in the chest were minimal before death, quite severe alteration of the alveolar epithelium, sometimes with fibrinous exudate, was found post mortem The good colour noticed was presumably due to CO_2 retention A raised CO_2 tension increases the dissociation of oxyhæmoglobin and relaxes arterioles, thus producing a warm pink skin Here, then, was another problem to be solved, because attention to the chest at a later stage, when signs were obvious, failed to save these patients Thus we did by further extending tracheotomy to any patient with severe head injury who was unconscious, immediately we realised that there was, indeed, in the majority, a large amount of material which could be sucked out of the bronchial tree, immediately after admission In some cases this consisted of blood-clot or solid vomit which could not be dislodged by suction, and resort was had to bronchoscopy and actual irrigation of the affected part with the patient in Trendelenburg's position to ensure complete clearance of the material, even when tracheotomy was done Now, therefore, we view with suspicion all head-injury patients who are deeply unconscious on admission, and it is our policy to perform tracheotomies on all, unless they show imminent signs of returning consciousness If there is any doubt about the patient returning to consciousness, then an endotracheal tube is retained for twelve hours only, and failing a full return to consciousness at this period, a tracheotomy is carried out before the tube is removed The fact that most of our cases now never develop chest lesions is due to the promptness with which the tracheotomy is done As a rule these patients now survive and recover well

Operation of Tracheotomy

The operation is usually carried out under general anæsthesia with an endotracheal tube in position A transverse incision is used and a square opening made between the third and fourth rings of the trachea Suction is carried out (via a long rubber catheter), and, if necessary, bronchoscopy and irrigation A wide cuffed tracheotomy tube is used—as large as can be admitted to the trachea The patient is stimulated to cough to clear the chest as much as possible Suction is continued in the ward with actual stimulation of the patient by pushing the catheter well down into the carina area No complications of the operation have been noted The transverse incision heals well with little scarring, a longitudinal incision heals with a keloid scar, wide and tender

After tracheotomy, careful frequent aseptic suction must be carried out, and air or oxygen entering the tube must be warmed and moistened to prevent the secretion from hardening and blocking the bronchial tree It is also essential to carry out routine bronchoscopy daily at least, and more frequently if the patient is deteriorating, in order to remove clot or inspissated secretion Daily radiography of the chest is also essential to deal with partial or complete collapse of the lung

Treatment of Central Factors

We shall not here discuss in detail the rather complicated treatment of these patients from this point of view, since a complete review of treatment and results will be given in a later paper The principles are

(1) The use of chlorpromazine, promethazine, pethidine, and levallorphan in a "lytic cocktail" We believe that chlorpromazine coordinates the function of the damaged reticular material of the brain-stem, and the cocktail combats restlessness and controls rigidity of the limbs, as well as a rising temperature due to damage sustained by the temperature-regulating mechanisms

(2) Immediate transfusion of triple or quadruple plasma to prevent or treat cerebral œdema In our experience it will rapidly bring œdema under control

(3) Any rise in temperature due to pontine damage is dealt with by (*a*) the lytic cocktail as described, (*b*) exposure of the patient, or (*c*) the use of wet sheets, an open window, ice bags, or a refrigerating machine

Our whole idea is not to produce hypothermia, thus cutting down cerebral circulation and the oxygen supply to damaged cells which would do harm, but to ensure that as normal a temperature level as possible is maintained and death from a rising hyperthermia prevented

(4) In addition, it is important to avoid oral feeding while a patient is unconscious

(5) Physiological tensions of oxygen and CO_2 must be maintained in the blood

(6) Fluid and electrolyte balance and caloric intake must be maintained.

By these methods satisfactory progress has been achieved, but more could be done It is not sufficient to tackle this problem at a special head-injury centre, because it exists from the time the accident takes place, and it should be tackled as soon as possible after the accident Unfortunately, only too often, it is tackled too late or not at all

Treatment Outside the Head-injury Centre

Transport to Hospital from the Site of the Accident

We are appalled to find that many ambulances have a driver only and have no-one to look after the patient, reliance being placed on the presence of relatives or the police There is obviously here a place for a medical officer of the intern type, as in the United States, or for a fully trained nurse to accompany the ambulance to the site of any accidents—suction apparatus, oxygen, and blood also being carried

Too often the patient is transported lying flat on the back, blood, cerebrospinal fluid, or vomit has free access to the trachea in an unconscious patient with disorganised pharyngeal or laryngeal function In the absence of a cuffed endotracheal tube, only gravity can keep foreign material out of the lungs and a position must be adopted to ensure that the effect of gravity will prevent aspiration from above and assist in the drainage of obstructive secretions This can be done by the adoption, as a routine, of either the semiprone position with a Trendelenburg tilt of 20°, or a knee-elbow position on cushions where there is severe drainage of blood or cerebrospinal fluid from the nasopharynx Without endotracheal intubation or tracheotomy, adequate suction of the bronchial tree is impossible, but attempts to stimulate the cough reflex by pharyngeal intubation in some cases may be effective

Arrival at a Casualty Department of a General Hospital

Adequate attention to the above points is essential and immediate suction and oxygen should be given The receiving-officer has then to decide whether the patient is to be transferred to a head-injury centre or to be admitted If this patient is to be sent on, the details mentioned in the last paragraph must be attended to If the patient is to be transferred any distance, intubation should be considered if his natural responses are insufficient (or likely to become insufficient) to maintain a free airway and to enable secretion to be removed

In the deeply unconscious patient intubation is easy and should be a routine to ensure a free airway and to avoid the ill effects of vomiting during transport In the semiconscious patient, who will still respond to stimulation, introduction of the tube is not so easy, and this should be done by a trained anæsthetist It should be done in every case with drainage of blood and cerebrospinal fluid, or where it is suspected that vomit or blood has already been aspirated A cuffed tube, to prevent aspiration of foreign material, appears to be tolerated better than an uncuffed one This may be because the inflative cuff prevents friction between the tube and the tracheal wall during respiratory movements, which may be accentuated in conditions of respiratory distress It should be remembered that coma may deepen during transport and that at any time there may be copious vomiting The stomach contents should, therefore, be aspirated before transport A tube passed at this early stage and maintained for some hours may obviate the necessity for tracheotomy in patients who make a rapid return to consciousness We have noted that patients protected in this way from anoxia before admission usually make a more full recovery than similar patients who have been allowed to become cyanosed and dyspnœic from preventable respiratory obstruction, and this recovery is rapid.

If an anæsthetist cannot accompany the patient, the services of a doctor or specially trained nurse will be required He must know how to diagnose respiratory insufficiency, how to avoid aspiration of blood or vomit, how to perform adequate pharyngeal and tracheal suction, how to administer oxygen correctly, and above all how to keep the airway patent by holding the chin correctly, or by using a pharyngeal or nasopharyngeal airway if the patient is not intubated

Local Unit

If the patient is not fit to travel immediately and is to be held at the local hospital, the above measures must be carried out Intubation is only a temporary measure and tracheotomy should be done as soon as possible with adequate suction and oxygenation The central factors must be dealt with by the principles previously described

Summary

Of those who survive the accident itself, the main cause of death in patients unconscious after head injury is respiratory insufficiency and anoxia The anoxia is due to central disturbances of the control of respiration, and reduction of compliance of the lungs by blockage or irritation of the bronchial tree by aspirated material and by retention of mucus

A regime must be used similar to that laid down for bulbar poliomyelitis

Correct posture to prevent seepage into the lungs and tracheobronchial tubes

Temporary intubation

Isolation of the lungs from the disorganised pharynx by early tracheotomy

Their further protection by continued aseptic tracheobronchial toilet

The use of a lytic cocktail to coordinate the reticular mechanisms of the brain-stem, and control rigidity, restlessness, and hyperthermia.

Avoidance of oral feeding during unconsciousness

Maintenance of physiological tensions of oxygen and CO_2 in the blood

Maintenance of fluid and electrolyte balance and caloric intake

Combating of infection by use of antibiotics

Relief or prevention of secondary cerebral œdema by use of intravenous triple plasma

It is not enough to wait until the patient reaches a special centre The important factor is treatment along these lines as soon as possible after the accident.

If proper attention is given to respiratory insufficiency early enough, many patients previously considered hopeless will survive In our experience the mortality has already been lowered, in these cases, from 90% to below 40%, and with further improvement in technique it can probably be lowered to 20%

The important fact, too, is that not only will the majority who survive make a good physical recovery, but they will also make a rapid return to a nearly normal mental state and will not end up as mental defectives, a burden to themselves and the community In fact, many will be able to return to productive work

REFERENCE

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THE HOSPITAL URINE BOTTLE AND BEDPAN AS RESERVOIRS OF INFECTION BY PSEUDOMONAS PYOCYANEA

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The possibility of establishing the sources of infection with *Pseudomonas pyocyanea* by immunological and bacteriophage typing of strains of that microorganism has been examined by Gould and McLeod (1958), who conclude that the correlations observed are in a large measure significant, indicating the probability that endemic persistence of *Ps pyocyanea* in surgical wards may be responsible for much of the infection of this kind which often follows catheterisation and operations on the urinary tract Such infections have been reported in hospitals in many different parts of Britain (Shackman and Messent 1954, Pyrah et al 1955, Gillespie 1956, Dutton and Ralston 1957) and appear to be as common in Edinburgh as elsewhere

It was therefore decided to investigate the ways in which *Ps pyocyanea* infection may be carried and persist

Method

Certain wards, apparatus, and personnel of three hospitals in which *Ps pyocyanea* infection had been observed were systematically examined Similar investigations were also made, in so far as they were pertinent, in the laboratory in which the work was being done, to check the possibility that accidental laboratory contamination might be responsible for some of the observations made

The methods of isolation and identification of the microorganism are discussed by Gould and McLeod (1958) and, apart from special detail, will not be considered here, but to make clear the significance of the following observations their findings are briefly summarised as follows

In each of the three hospitals there was an outstanding type of *Ps pyocyanea* strain differing from those outstanding in the two others, both in its reactions to agglutinating sera and its bacteriophage sensitivity The variety outstanding in hospital A has been described as of agglutination type α and phage-type N, that in hospital B as of agglutination type β and phage-type J, and that in hospital C as of agglutination type γ and phage-type QS There were also several strains of mixed agglutination and phage types

Results

The material examined for *Ps pyocyanea* and the frequency with which the organism was isolated from these various sources are set out in table I

Dust

Two methods were used in looking for dust infection one was to run a few drops of sterile broth on to floor, window ledge, or whatever surface was under investigation and to suck this up again after a short interval (one or two minutes at the most) and to distribute the fluid so obtained to suitable media, and the other was to leave plates of media exposed under ward beds for two hours, including a time of bed-making

Ps pyocyanea was not recovered from the laborator bench or floor, although both were undoubtedly con taminated with infected urine, and sometimes with spilt cultures, repeatedly in three years

On one occasion two colonies diffusing green pigment were observed These, however, differed from the strains isolated from patients in their inability to grow well or to form pigment at 37°C, their failure to produce chloroform-soluble pyocyanin and the absence of response to any of the agglutinating sera or bacteriophage preparations which we had at our disposal

The observations on hospital ward dust were, with one exception, negative The exception was the ward floor immediately adjacent to an open bottle to which urine was draining from a Foley catheter (drainage to open bottles was abandoned soon after this investigation started) It was considered, however, that this could not be accepted as an example of persistence in dust but that it was rather evidence of a very recent contamination with infected fluid

Sinks and Wash-basins

A few ward wash-basins and the laboratory sinks were investigated by transfer of residual fluid to suitable media, and *Ps pyocyanea* was isolated once from both of these sources

The fact that *Ps pyocyanea* had been detected in laboratory sinks and ward wash-basins suggested that the water-supply might be contaminated, so water from the

TABLE I—RESULTS OF EXAMINING MATERIAL

Material	Sources	Total number of examinations	Strains of *Ps pyocyanea* isolated
Not yielding Ps pyocyanea			
Dust	2 wards in hospital A, 1 ward each in hospitals B and C, and laboratory in which work was done	52	1*
Water	Water supply in hospitals A and C, including samples from main and 5 storage tanks	8	0
Catheter lubricants	Samples taken in hospitals A and C	4	0
Blankets	Hospital A	4	0
Urine of men free from symptoms of urinary-tract infection	Group of male medical students	40	0
	Male patients attending surgeries in general practice	123	0
Yielding Ps pyocyanea occasionally			
Waste water	Laboratory sinks	3	1
	Ward wash-basins	3	1
Skin secretion	Hands of surgeon, nurses, and ward orderlies	10	1
Urine of patients free free from symptoms of urinary-tract infection	Patients in medical wards	104	4
	Patients in surgical wards in which little urological work was done	73	4
Bowel contents post mortem	Ileum	7	0
	Cæcum	7	0
	Sigmoid flexure	7	1
Yielding Ps pyocyanea frequently			
Urine in wards active in urological surgery	Open drainage to bottles receiving flow from indwelling catheters	3	3
	Patients normal in respect of their urinary tract but nursed in wards doing much urological surgery	135	25
	Patients with indwelling catheter before or after surgical operation on bladder	98‡	60
Urine bottles	In ward doing occasional urological surgery	10	3
	In ward doing much urological surgery	44	30
Bedpans	In wards doing much urological surgery	21	4†

Nutrient agar, serum-agar, 0 4% 'Dettol'-agar, and chopped-meat broth were used, the last being transferred from the plate to a tube before incubation These plates were not, however, intentionally left in the immediate vicinity of a patient infected with *Ps pyocyanea*

* This strain was recovered from the floor beside an open urine bottle to which a *Ps pyocyanea* infected urine was draining

† One of these strains gave weak agglutination and was insensitive to bacteriophage

‡ Number of patients most of whom had repeated examinations of urine over a considerable period.

mains and storage tanks was drawn from the taps and investigated Growth was obtained from all these samples, but no *Ps pyocyanea* was detected in any of them

Fluids used for Bladder Lavage

In one hospital, at one stage in the investigation, strains presenting the general characters of *Ps pyocyanea* were recovered from the fluid used for postoperative lavage of bladders The source appeared to be defective methods of sterilisation at the dispensary where these fluids were prepared They did not appear after these methods had been revised

Blankets

In one ward in which there was a good deal of *Ps pyocyanea* infection blankets returned from the laundry and others which had been used recently in giving patients bed-baths on admission were investigated. The method adopted was to use a fold of the blanket as a filter for nutrient broth, some of which was recovered after traversing the blanket A considerable variety of coccal and bacterial forms as well as anthracoid bacilli were recovered in such filtrates but no strain of *Ps pyocyanea*

Lowbury and Fox (1954) reported that *Ps pyocyanea* was recovered from floor and blanket dust in wards in which patients with infected burns were being nursed Pyrah et al (1955) also recovered *Ps pyocyanea* from dust and bedclothes in the vicinity of cases of urinary-tract infection with *Ps pyocyanea* during a severe outbreak of such infection in a ward where dettol was used for sterilising urine-bottles, nail brushes, &c (dettol was shown subsequently to be ineffective for this purpose)

Our own observations suggest that dust is not a usual source of such infection, that *Ps pyocyanea* dies off rather rapidly when dried, and that it persists only where it has access to fluid

External Genitalia and Anterior Urethra of Healthy Males

The suggestion from this preliminary work, that *Ps pyocyanea* did not readily persist in dust but would be more often found in contaminated fluids, led us to seek the answer to the following question *Does Ps pyocyanea form any part of the flora of the external genitalia and anterior urethra in the healthy male?*

Since there is much evidence of the common appearance of that microorganism in the urinary tract as a sequel to catheterisation, cystoscopy, and operations, it obviously might so appear only because bacteria commonly present in the anterior urethra or on the external genitals are inevitably carried up to the bladder by any instrument introduced

An attempt was therefore made to determine the extent to which this bacterium occurred in the urine of patients whose genitourinary tract was apparently healthy, and whether, in this respect, one ward differed from another

For this purpose samples of urine were collected from most of the male wards in a large general hospital

Since it is recognised that there is normally a bacterial flora of the anterior urethra, and since no antiseptic was available which was capable of exercising a rapid bactericidal effect on bacteria and yet was sufficiently mild to cause little pain or irritation when applied to the delicate epithelium of the surfaces in question, it was considered that the course least open to objections was to issue to each patient a sterile flask whose neck was protected by an inverted glass beaker The total specimen of urine was obtained in this flask much as if it had been passed to one of the urine-bottles in use in hospital wards No sterilisation of the surface of the penis or of the anterior urethra was attempted The flask was covered again by the glass beaker as soon as it had been used and it was then transferred to the laboratory for investigation

Ward observations—All these investigations were made in one hospital, and the results are given with detail of antigenic bacterial types in table II

5 ml samples of the urine were transferred to tubes containing either broth or 0 30% dettol broth, or 0 03% brilliant-green broth. Broth in bulk was then added to the residual urine in the flask, roughly in the ratio of 1 part of broth to 3 parts of urine, and all four cultures were incubated and observed directly and by subculture to agar for three days

Several points are suggested by the results One of these is that there are strains of *Ps pyocyanea* which have become endemic in certain wards, especially those considerably engaged in urological surgery, whereas in most medical wards and some surgical wards either no *Ps pyocyanea* is found at all in the patients' urine or mostly strains other than the type endemic in wards active in urological surgery Another feature is that many of these infections are transient—i e, a second examination of the patient's urine does not reveal any *Ps pyocyanea* An example of this is medical ward M3 (table II)

In this ward *Ps pyocyanea* was found in the urine of 3 patients, and all were of the same antigenic type β/J, but, on subsequent examination, continuing infection was found in

TABLE II—RESULTS OF EXAMINING PERSONS

Source	No of patients whose urine was examined	No of isolations of *Ps pyocyanea*	Agglutination and phage type	Repeat examinations	Agglutination and phage-type
Series I—Surgical wards					
S1, neurological	12	1	α/N	Neg	
S2, general and urological	44	3	α/N 2 lost 1	Not done	
S3, „	45	7	α/N 6 β/J 1	1 neg 5 not done Not done	
Series II—medical wards					
M1	23	—	—	—	—
M2	20	1	α/BSG	Pos	α/Nil
M3	18	3	β/J	2 neg 1 pos	β/J
M4	17	—	—	—	—
M5	26	—	—	—	—
Series III—male students and males attending surgery of general practitioner	100	—	—	—	—
Series IV—surgical wards					
S2	15	9	α/N	5 not done 1 pos (twice) 3 neg	α/N
S3	31	6	α/N 5 β/J 1	1 neg 1 not done 3 pos Pos	α/N* β/J
S4 orthopædic	14	—	—	—	—
S5, vascular and general, including some urological work	16	—	—	—	—
S6, general and occasional urological cases	15	—	—	—	—
S7, thyroid and general surgery	16	3	β/J 1 α/N 2	Pos (twice)† Both neg	β/J
Series V—male patients attending surgery of general practitioner	63	—	—	—	—

* In 2 of these cases the urinary sediment in the last specimen of urine taken which was positive for *Ps pyocyanea* was examined but gave no frank evidence of infection of the urinary tract No leucocytes or red blood-cells were detected There was epithelial debris and in 1 case also bacteria

† Contains mucus and oxalate crystals but no leucocytes or red blood-cells were detected.

one of these cases but not in the two others Further, in the surgical wards in which *Ps pyocyanea* infection was endemic the same strain might be recovered repeatedly from a patient confined to bed and using bottles and bedpans for his excretions, notwithstanding the fact that he had no symptoms of urinary infection and was passing urine free from any cellular elements suggesting a pathological condition of his urinary tract

A particularly interesting case of this sort was a young man with a fractured thigh nursed in a ward in which much urological surgery was done His urine yielded *Ps pyocyanea* on four consecutive occasions in six weeks, but the centrifuged sediment of his urine showed no cellular exudate suggesting inflammation of his urinary tract

Since a system of immersion of the urine-bottles in the ward in a carbolic bath had been instituted after the first two examinations, contamination from this source could not be held to explain the presence of *Ps pyocyanea* in the last two specimens taken, and it was thought that the appearance of *Ps pyocyanea* might be due to infection by contact with the bedpan Closer investigation of the patient, however, revealed that he had a chronic aural discharge, which proved to contain both *Ps pyocyanea* and *Proteus* sp

It is obvious that this patient might well have been responsible for a considerable amount of *Ps pyocyanea* infection of the ward urine-bottles before the antiseptic-tank technique was adopted

Observations outside hospital—No culture of *Ps pyocyanea* was obtained in the examination of 123 men free from urinary symptoms and attending as outpatients at the surgeries of general practitioners in the city which supplied a large proportion of the patients attending the hospitals under investigation In addition, the urines of 40 male students were investigated and these also were negative

These observations furnish good evidence that *Ps pyocyanea* is not a commensal, unless very exceptionally, in the urethra, bladder, or external genitals of the healthy male They also make it altogether improbable that contamination within the laboratory was responsible for the positive results recorded, since so long a series of negative results could not have been obtained if the laboratory technique had been at fault

Stools

In attempting to determine the normal incidence of *Ps pyocyanea* in patients' stools the obvious possibilities of cross-contamination in the wards had to be taken into account, and it was necessary to eliminate as far as possible all external sources of contact

The most effective method of doing this appeared to be to take samples from the gut post mortem After the abdomen had been opened, therefore, the ileum, cæcum, and sigmoid flexure were exposed successively, and, after the surface had been seared with a large heated copper spatula, a Pasteur pipette was driven into the gut and a specimen of content withdrawn

Of 7 cadavers examined in this way only 1 gave a positive result, and in this case *Ps pyocyanea* was recovered from the sigmoid and not from the higher sections of the bowel A much extended observation is obviously necessary to establish any reliable figure, but it seemed that this microorganism, although not particularly common in the gut, might be one of the ultimate sources of the strains which give trouble in urological surgery

A systematic examination of all specimens of stools received in the university laboratory had been made by J C Gould (personal communication) during this investigation and had revealed the presence of *Ps pyocyanea* strains in 4 of 97 stools examined

Urine-bottles

In seeking further for an answer to the question how *Ps pyocyanea* infection is maintained and passed from one patient to another in hospital wards, it was felt that the observations already described made it altogether unlikely that dust was largely responsible All our observations pointed to some reservoir in which moisture was always available and to urine and stools as potential sources of infection

Attention was therefore turned to the methods of disposal of excreta in the wards A ward was selected in which it was known that several cases of prostatectomy with mixed infections, including that by *Ps pyocyanea*, had recently been under treatment The results were rather surprising The practice in this ward, as in many others, was that each patient had his own urine-bottle These were emptied to a sluice, thoroughly rinsed with running water, and returned to the patients' lockers, and, at intervals, these bottles were sterilised

With the cooperation of the ward orderly all the urine-bottles in the ward were brought under investigation after being cleansed in the usual way This was done first when several patients who had recently undergone prostatectomy were known to be infected with *Ps pyocyanea* Since these patients were all draining by Foley catheter in a closed circuit to bottles of Winchester type containing 'Hibitane' as antiseptic and protected from contamination by dust by an antiseptic air-trap for exit of air from the bottle, they would not be liable to infect the ward urine-bottles directly until they began passing urine in the normal way after removal of the Foley catheter

The urine-bottles were examined with the same media as were used for all examinations of patients' urine

5–10 ml of nutrient broth was run into the urine bottle, and after agitation of the bottle the broth was sucked up and divided between three tubes containing either nutrient broth, nutrient broth with 0 30% dettol, or nutrient broth containing 0 03% brilliant green These tubes were incubated for three days and then plated out on nutrient agar Characteristic colonies diffusing green pigment were picked off If such did not appear, the growth which developed on the agar plate was overrun with tetramethyl *p*-aminobenzene HCl solution, and, *if a positive* oxydase reaction was obtained, further plating to isolate oxydase-positive colonies for study was done

In the first investigation seventeen bottles, each of which was marked with the patient's name and retained for his sole use (the usual practice in the ward), were examined after rinsing Three spares, which had not been in use for some time, were also examined, but no bottle used by a patient known to have an abnormal urinary tract was included *Ps pyocyanea* was recovered from seven of the seventeen bottles in use, and in every instance it was of the α agglutination, N phage-type—i e, that responsible for almost all the postoperative infections in the ward

A second series was investigated three weeks later, and on this occasion three of four spare bottles and all twenty bottles in current use were found to be infected with *Ps pyocyanea* All twenty-three strains were shown to be of the α agglutination type, and twenty-two of these were of the N phage-type, the exception not showing any phage sensitivity

A third investigation was made in another ward, in which a limited amount of urological surgery was done Here the investigation, made earlier in the same week, of the urines of patients with a supposedly healthy urinary tract, had not revealed any *Ps pyocyanea* infection, although it was found in the urine of a patient who had had an amputation of the penis because of a tumour

In this ward ten urine bottles were examined, six in current use and four spares *Ps pyocyanea* was recovered from three of these, and the strains were of agglutination type α and phage-type N That from the patient whose penis had been amputated was of mixed agglutination and unusual phage type

Bedpans

The bedpans, which had been cleansed and were lying ready for issue, were examined in the two wards in which most urological surgery was done

In one of these wards all the bedpans in current use were examined repeatedly at intervals of a few days, twelve examinations being made *Ps pyocyanea* was isolated on three occasions; all were of α/N type

In the second ward ten investigations of this kind were made, but in only one was *Ps pyocyanea* isolated, and this was a doubtful strain, being a poor pigment producer, insensitive to phage, and giving only weak agglutination with α-type antisera In other respects (good growth at 37°C, fermentation of glucose without gas but not of lactose, saccharose, dulcite or mannite, absence of indol, positive oxydase reaction; and characteristic morphology and staining) it resembled *Ps pyocyanea*

Hands of Staff

The hands of one surgeon, two nurses, and several male orderlies were investigated by rinsing in sterile nutrient broth and subsequent cultivation of the broth

In one instance the hands of an orderly were investigated at 8 A M, just after he had come on duty, and again at three-hourly intervals during the day *Ps pyocyanea* was isolated only once in this series, it was in the broth in which the orderly's hands were rinsed shortly after coming on duty

Both in the examination of the cultures from bedpans and in those of the hands of the staff bacteria were isolated which closely resembled *Ps pyocyanea* but never produced green pigment in a convincing way Many descriptions of such bacteria have been published (Sandiford 1937, Gaby and Free 1953), and it is possible that these were strains modified in their metabolism by contact with antiseptics

Discussion

It is obvious from these results that nurses and orderlies required to empty and rinse urine-bottles and bedpans in wards active in urological surgery will inevitably infect their hands repeatedly with *Ps pyocyanea* Hence they are a source of danger to any patient whose bladder and drainage or lavage apparatus they have to manipulate. It seems altogether probable that much of this infection could be cut out by a proper use of antiseptics This would involve storing in an antiseptic tank all urine-bottles and bedpans not in use and issuing bottles for use only from such tanks and with a residuum of antiseptic solution—about a fifth of the capacity of the bottle—which would be sufficient to sterilise the bacteria excreted by the patients even when diluted fourfold by urine

The sterilisation of the stool by residual antiseptic in the bedpan is more difficult, but the danger of infection from these vessels could be largely eliminated if two procedures were regularly followed The first of these would be sterilisation of the bedpan, after cleansing, by a brief immersion in boiling water or a longer one in an antiseptic bath The second would be that the nurse or orderly handling bedpans should do so only when wearing rubber gloves, and if these, while still on the hands, were cleansed under running water and then rinsed with spirit or, better, a 2% concentrate of hibitane before they were removed, the contamination of hands would be cut down to a minimum Complete destruction of bacteria such as *Proteus* spp and *Ps pyocyanea* in periods of a few minutes is not easily attained with any antiseptic. It must be specially emphasised, as has already been done by Pyrah et al (1955), that dettol is not an efficient antiseptic for the destruction of *Ps pyocyanea*—a finding which has been amply confirmed in our own observations Cetrimide (the active principle of 'Cetavlon') is also unsuitable These substances can be usefully incorporated in media to separate *Ps pyocyanea* from mixed infections (Harper and Cawston 1945, Lowbury 1951, Gould and McLeod 1958)

Hibitane 0 2% and carbolic acid 2% are both effective, however, in killing off *Ps pyocyanea* and other forms likely to infect the urinary tract which are found in urine-bottles

This is not a case in which asepsis is practicable or enough—sterilisation of urine-bottles and bedpans will not meet the case They must contain antiseptic when issued if continual infection of the hands of the attendant on the patients is to be avoided

Conclusions

Infections with *Ps pyocyanea* appear to be, in a large measure, hospital infections This bacterium easily adapts itself to the human urinary tract, especially in the presence of protein exudate such as must inevitably be present after operations on the bladder

It is *not* a commensal of the normal external genitalia of the male and is not therefore unavoidably introduced in such procedures as catheterisation. It does not readily persist in the dry state and is only found in dust exposed to recent heavy contamination

The apparatus in normal ward use in which it can most readily persist is the urine-bottle and the bedpan Since the hands of nursing personnel are inevitably contaminated by handling and rinsing these vessels, it is not enough to issue sterile bottles and pans Elimination of infection in all vessels used for the collection of excreta should be assured by an efficient use of antiseptics as described above For these purposes dettol and cetavlon are unsuitable because they are not effectively bactericidal against one of the strains of bacteria met in the post-operative infections of the urinary tract—i e., *Ps pyocyanea* Carbolic acid as a 2% solution and hibitane as 0 2% solution are among the antiseptics which are adequate. Carbolic acid is cheaper

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CYTOLOGICAL DIAGNOSIS IN GYNÆCOLOGICAL PRACTICE

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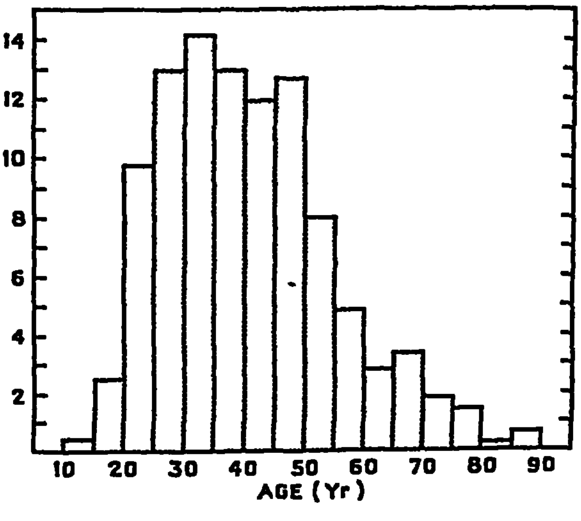
For the past five years in this professional unit cytological examination of the vagina has been added to our routine clinical examination of outpatients The technique is in the hands of one of us (M E A), who has trained technicians to share the work After about six months' training an apt pupil may become reliable and, when deemed fit, signs the cytological report on his or her responsibility The great disadvantage in the technique is that careful microscopic screening of a vaginal pool smear may take 15–20 minutes (average 5–7 minutes)

This paper follows our preliminary report (McLaren et al 1956) and gives a four-year summary, with our interpretation of the value of the technique when closely integrated into gynæcological practice

Clinical Material

4250 consecutive outpatients were examined, of whom 85 (2%) had malignant disease of either the body or the cervix of the uterus The age-distribution shows that the bulk of the patients were of reproductive age (see figure)

The clinical team, who were experienced gynæcologists, tried to set a high standard of clinical diagnosis, using a specially designed case-sheet for every patient with the object of recording suspicious findings For example, note was made of any bleeding apart from menstruation—e g, postmenopausal, intermenstrual, and postcoital bleeding—the cervix was exposed whenever possible, and a diagram was made of the portio vaginalis to show any erosions and bleeding areas 481 (11%) patients were labelled as "suspect—for careful investigation in hospital", of whom 85 were proved to have malignant disease carcinoma of the cervix in 53 and either carcinoma or sarcoma of the corpus in 32



Age-distribution of gynæcological outpatients

To assess the accuracy of cytological diagnosis we compared it with our clinical diagnosis, which of course is not 100% correct—e g, the exploring curette may miss a small carcinoma, and a cervical biopsy may possibly miss a very small area of invasive carcinoma or of carcinoma-in-situ The results are shown in table I

Of the 53 patients with invasive carcinoma of the cervix the smear was positive in 50 (94%) Of the 3 remaining smears 1 was labelled "suspicious—please repeat", and 2 were cytological errors which were quite obvious on review Of the 32 patients with either sarcoma or carcinoma of the corpus the smear was positive in 25 (78%), the remaining 7 being labelled as suspicious or inadequate

Invasive Carcinoma Discovered by Cytological Examination

An experienced clinical team failed to diagnose uterine cancer on 3 occasions, when it was present, an incidence of about 1 in 1500 patients The 3 cases provided positive smears, which fact led to further investigation

TABLE I—ACCURACY OF CYTOLOGICAL DIAGNOSIS IN CASES OF KNOWN INVASIVE NEOPLASM

—	Series A* (1952–54)	Series B (1954–56)	Total
Outpatients	2250	2000	4250
Cervix			
Carcinoma	34	19	53
Smear positive	33	17	50
Efficiency of cytological diagnosis			94%
Corpus			
Carcinoma	14 } 16	14 } 16	32
Sarcoma	2	2	
Smear positive	12	13	25
Efficiency of cytological diagnosis			78%

* Already reported (McLaren et al 1956)

Case 1 —A married woman, aged 34, 2-para, had menorrhagia, which was investigated by curettage, the clinical findings being negative A positive smear was nevertheless obtained, but she left Birmingham without being fully investigated and could not be traced for twenty-one months She had by then a small carcinoma of the portio vaginalis At Wertheim's hysterectomy no involvement of lymph-nodes was found, and she has remained well for four years

Case 2 —A married woman, aged 42, 2-para, was placed on our waiting-list for repair of prolapse A positive smear led us to expedite her admission and to re-examine her cervix under general anæsthesia, when a small area of carcinoma on the posterior cervix was found which was only obvious on pulling down the cervix under anæsthesia The patient was considered to be unsuitable for radical surgery, so she was given radium treatment, with an apparently good result lasting at least two years

Case 3 —A married woman, aged 62, 2-para, reported with postmenopausal bleeding She was very obese, with a small uterus "frozen" in the pelvis, possibly as a result of a high amputation of cervix and plastic repair We therefore hesitated to remove her uterus without proof of malignant disease Curettage on two occasions was negative Repeatedly positive smears, however, expedited the operation which would have been necessary on clinical grounds for persistent postmenopausal bleeding As expected, her operation proved to be very difficult, a submucous fibroid had apparently excluded a small adenocarcinoma from the exploring curette The patient has remained well for four years

Errors in Cytological Diagnosis

False Positive Smears

A false positive smear is defined as a positive cytological report where routine curettage and a ring biopsy (excision of the squamocolumnar junction and part of the lower cervical canal) or histology of the uterus removed at hysterectomy does not reveal either uterine carcinoma or carcinoma-in-situ

The incidence of false positive smears is given in table II, which shows an error of 16% In practice this error means that, in four years, our Unit had to admit only 16 cases for full investigation (including ring biopsies) in which no significant lesion was found

TABLE II—FALSE POSITIVE SMEARS

—	Series A (1952–54)	Series B (1954–56)	Total
No of patients	2250	2000	4250
No of positive smears	54	40	94
No of false positive smears	6	10	16

False Negative Smears

A false negative smear is defined as a negative cytological report when investigations reveal either invasive carcinoma or carcinoma-in-situ

The incidence of false negative smears is given in table III, which shows that there were 11 (10%) false negative smears Smears were reported negative in 3 of 53 patients with obvious carcinoma of the cervix In retrospect 2 smears were obvious errors in microscopic screening and 1 had been labelled as " suspicious—please repeat "

In 7 of 32 cases of carcinoma of the corpus smears were reported as negative In the vaginal-pool technique this error is apparently inevitable, partly because there is no constant supply of malignant cells in the vagina, perhaps owing to stenosis of the cervical canal, or more commonly because of massive dilution of a few malignant cells with blood

Borderline Smears

In the early days of our work on cytological diagnosis borderline smears were common and demanded further smears and further clinical study We did not, however, admit all patients with suspicious smears for curettage and ring biopsy With growing experience and confidence in cytological diagnosis these " suspicious—please repeat " smears became fewer For example, in series A (1952–54) there were 128 (5%), but in series B (1954–56) there were only 54 (2 5%) For this assay of cytological diagnosis we regarded borderline smears as negative Repeat smears were taken in most of the borderline cases and a further clinical report provided

Clinical Investigation Following Cytological Report

In clinical practice a negative smear must be ignored—e g , postmenopausal bleeding must be fully investigated in the theatre irrespective of the cytological report On the other hand, with our knowledge of the accuracy of cytological diagnosis a clinician may not ignore a positive smear The following investigations are obligatory

(1) Careful curettage of the endometrium and the cervical canal

(2) Ring biopsy of the apparently normal cervix—i e , a biopsy specimen cut by a sharp knife to the shape of a dunce's cap to include the whole squamocolumnar junction and much of the lower cervical canal The specimens are then prepared for pathological studies which may necessitate serial sections of portions of the cervical biopsy specimen

TABLE III—FALSE NEGATIVE SMEARS

—	Series A (1952–54)	Series B (1954–56)	Total
No of smears	2250	2000	4250
Invasive carcinoma			
No of proved cases	50	35	85
No of related false negative smears	5	5	10
Carcinoma in situ			
No of proved cases in situ	9	7	16
No of related false negative smears	1	0	1

Cervical Carcinoma-in-situ

The histological diagnosis of carcinoma-in-situ is often difficult and depends on personal interpretation

Many lesions fall within the strict criterion—when the entire thickness of the squamous and in parts columnar epithelium is replaced by malignant cells—and these we have called typical carcinoma-in-situ On the other hand, certain forms of abnormal cellular hyperplasia, though otherwise similar, may show maturation of the superficial squamæ Such a lesion, though not falling into the strict definition of carcinoma-in-situ, may strongly suggest malignant intra-epithelial change, sometimes more than the typical lesion Such lesions we call " equivocal carcinoma-in-situ " This epithelial change is quite distinct from simple epidermisation, which itself may give rise to bizarre patterns but is recognised as benign metaplasia by the experienced pathologist Galvin et al (1955) describe three grades of basal-cell hyperplasia of the cervical epithelium and conclude that the third stage may progress to carcinoma-in-situ, although regression can take place (Peckham et al 1954) We have seen equivocal carcinoma-in-situ merge into typical carcinoma-in-situ

It is certain that cytological examination does not pick up all carcinoma-in-situ—e g , in this series we took a random biopsy specimen of an apparently innocent erosion which had yielded a negative smear, histology revealed definite carcinoma-in-situ Nevertheless, since random biopsies are not included in our routine outpatient investigations, we can record that at present, the incidence of carcinoma-in-situ, diagnosed cytologically in our outpatient service, is almost 4 per 1000

Treatment of Carcinoma-in-situ

The natural history of carcinoma-in-situ is not yet understood It is, however, known that it can become truly invasive, involving lymph-nodes (Petersen 1955, Fletcher 1954) Complete removal of all carcinoma-in-situ is therefore obviously a method of preventing the subsequent development of cervical carcinoma A young woman, however, may desire children, and it is natural for the clinician to seek out a conservative method of treatment which will preserve the function of the uterus without exposing the patient to a risk of fatal carcinoma

Conservative therapy is supported by the observations of Peckham et al (1954) and Epperson et al (1951), who showed that a carcinoma-in-situ might disappear spontaneously

Petersen (1955) has followed up 127 patients with carcinoma-in-situ for as much as ten years and has found that a third of them ultimately developed invasive carcinoma of the cervix

Our own experience of therapy is limited both in numbers and in length of follow-up All our patients with positive smears undergo curettage and ring biopsy which may cure carcinoma-in-situ and allow prolonged follow-up study with further clinical and cytological examination On the other hand, a ring biopsy may not be adequate therapy, and more radical treatment then becomes necessary

Ring Biopsy and Follow-up

Of our 16 patients with carcinoma-in-situ 9 were treated by ring biopsy, and at present they are under

TABLE IV—INCIDENCE OF CARCINOMA-IN-SITU

—	Series A (1952–54)	Series B (1954–56)	Total
Total	2250	2000	4250
Typical carcinoma-in-situ	5	4	9
Equivocal carcinoma in-situ	4	3	7

observation with three visits to the clinic each year or more often if there is need. 6 patients have been followed up for more than eighteen months and 3 for more than three years.

A ring biopsy amounts to removal of a cone-shaped part of the portio vaginalis and lower canal, so in our unit we keep the patient in hospital from eight to ten days, for fear of secondary hæmorrhage. The cervix looks perfectly normal in about three months, normal mucous secretion may be expected with normal function and perhaps conception in the sexually mature woman. 2 of our patients conceived after ring biopsy, 1 proceeding to term and the other aborting at three months. We did not consider that our ring biopsy had disturbed the upper cervical canal sufficiently to be a factor in the abortion. Had the cervix been amputated, however, as in a plastic repair for prolapse, this would almost certainly have been the important factor in causing the abortion.

A deep ring biopsy may therefore be an adequate form of therapy.

Radical Ablation

Three radical hysterectomies with gland dissection (table IV, cases 4–6) were done because we felt that there was a real risk of invasive carcinoma coexistent with carcinoma-in-situ; in fact, we found only an in-situ lesion persisting in 2 and no abnormality in 1 specimen.

Simple hysterectomy was done in case 9, one of our first cases where the smears remained positive after a punch biopsy—i.e., a "therapeutic" ring biopsy (which we would now do) was replaced by hysterectomy in this patient, a woman aged 32 with four children.

In case 7 hysterectomy was done not for persistent carcinoma-in-situ after ring biopsy but after three years for severe menorrhagia.

We removed the uterus of a patient of 50 (case 10), whom we could not follow up adequately.

Teamwork and Need for Follow-up

The value of a weekly or twice-monthly conference of the members of the diagnostic team (clinicians, pathologist, and cytologist) has been proved repeatedly in our experience. The clinical notes and sections are also available for discussion, details of age, parity, desire for children, and the likelihood that the patient can be followed up before coming to a decision on therapy are established.

TABLE V—OPERATIONS FOR CARCINOMA-IN-SITU

Case no.	Age (yr.)	Reason for hysterectomy	Operation	Specimen
4	37	Widespread carcinoma-in-situ in patient who had already had carcinoma of vulva	Wertheim's	Residual carcinoma in situ
5	35	Smear +ve after ring biopsy	Wertheim's	No carcinoma-in-situ
6	51	Smears +ve 5 mos. after ring biopsy; at first she refused admission	Wertheim's	Residual carcinoma-in situ
7	42	Menorrhagia 3 yr. after ring biopsy	Hysterectomy	No carcinoma in situ
8	46	Smear still +ve 3 mos. after ring biopsy	Hysterectomy and bilateral salpingo-oophorectomy	Residual carcinoma-in-situ
9	32	Smear +ve after punch biopsy	Hysterectomy	Residual carcinoma in situ
10	50	Follow-up impossible	Hysterectomy	No residual carcinoma-in-situ

In more detail the following questions are put down for discussion at our weekly conferences.

(1) Has the clinician cut an adequate ring biopsy specimen for a diagnosis of carcinoma-in-situ, or is a further biopsy necessary?

(2) Is it possible to exclude invasive carcinoma from this specimen?

(3) Has the knife obviously cut across the carcinoma-in-situ so that positive smears may be anticipated from a residual lesion?

The decision on treatment, although made by the clinician, is based on information given by the pathologist and cytologist and then only after joint discussion.

Comments

Although cytology may be of value to the clinician in the diagnosis of invasive cancer of the uterus, our experience suggests that only rarely will the technique discover an unsuspected lesion. The most important use of cytology lies in its ability to lead the clinician to a diagnosis of carcinoma-in-situ in the clinically normal cervix. We are offered not only the prospect of a diagnosis of carcinoma-in-situ but also the opportunity to study the condition. In our Unit cytology has been closely integrated into the practice of gynæcology, and it has therefore been possible to make a full study of each case, to plan adequate therapy, and to arrange follow-up.

Cytology has therefore given us the opportunity of making a long-term study of carcinoma-in-situ, ultimately with the object of understanding its natural history. Any study of this kind where invasive carcinoma is a possible outcome inevitably raises an ethical problem so that removal of the uterus may often appear to offer an easy solution. From our limited experience, however, we have found that a deep ring biopsy may prove to be adequate therapy provided that follow-up is carried out by the clinician and cytologist. Conservative therapy is of course of special importance to the younger woman desirous of a child or further children.

Summary

The chief function of cytology is to lead the clinician to discover carcinoma-in-situ in the clinically normal cervix. The surprise positive or pick-up rate of this lesion in our gynæcological outpatients is 3·5 per 1000.

Cytology may also lead to a diagnosis of early invasive carcinoma of the cervix or of the corpus.

Of 16 cases of carcinoma-in-situ 7 were treated by hysterectomy or extended hysterectomy, 9 were treated simply by ring biopsy and careful follow-up.

Carcinoma-in-situ is rare and is related to the development of carcinoma. There is need for long-term research by clinicians, who should pool their experience over the coming years.

We wish to acknowledge the valuable work of our colleagues, Mr M. J. D. Noble, first assistant, and Dr R. B. Parker, lecturer, in the Department of Obstetrics and Gynæcology. We also wish to acknowledge the financial support and equipment given to us by the British Empire Cancer Campaign and finally the Royal College of Obstetricians and Gynæcologists, which asked us to carry out this study and provided considerable help through its Scientific Advisory Committee.

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THE NATURAL HISTORY OF MALIGNANT GRANULOMA OF THE NOSE

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MALIGNANT granuloma of the nose has been known to otorhinolaryngologists since its original description in 1897 by McBride. Cases have been recorded under this name (Woods 1921), and also as progressive lethal granulomatous ulceration of the nose (Stewart 1933), lethal midline granuloma (Williams 1949), and granuloma gangrenescens (Bergquist and Koch 1949, Breckenridge et al. 1954).

Usually in a young adult or in early middle age, the disease starts as a localised granulomatous lesion of the nose, paranasal sinuses, middle ear, or nasopharynx, and progressively destroys the nose, face, and pharynx with little apparent resistance. Death occurs from cachexia or severe hæmorrhage, rarely from meningitis. Histological examination shows necrotic granulomatous tissue and a non-specific cellular reaction; giant cells are not found, and no organism is consistently isolated. Friedmann (1955) describes this as the "classical" form of the disease, and notes the occurrence in some cases of diffuse systemic lesions accompanied by a widespread necrotising angiitis, which leads him to identify these cases with Wegener's (1936, 1939) granulomatosis. References to systemic lesions can be found (Bonne and Lodder 1929, Hall 1934, Greifenstein 1937, Bergquist and Koch 1949, and Alexander 1954), though Spear et al. (1956), reporting another case, conclude that the systemic nature of malignant granuloma is not generally appreciated.

In many cases a generalised vasculitis has been found, and several workers (Klinger 1931, Wegener 1936, 1939, Weinberg 1946, Stratton et al. 1953, Godman and Churg 1954, Walton and Leggat 1956, Friedmann 1955) have suggested that the disease may be a form of polyarteritis nodosa. Among 111 cases of polyarteritis nodosa reported by Rose and Spencer (1957) upper respiratory granulomata were an early feature in 5. Necrotising or granulomatous lesions, not demonstrably related to arteries, were seen in various organs.

Malignant granuloma is uncommon. In 1956 Spear et al. could find only thirty-nine reported cases with necropsy. We have observed four cases, which we describe here because they have led us to certain therapeutic conclusions which other observers may be able to try before we can.

Case-reports

Case 1.—A male Jamaican, aged 42, developed pain over the left maxillary antrum, with mucoid discharge from the left nostril, in April, 1954. Treatment by antral washouts and penicillin gave temporary relief, but symptoms recurred at about six-monthly intervals. In January, 1956, he began to have 4-day bouts of malaise, shivering, sweating and temperature up to 103°F, and he was admitted to hospital in June, 1956.

He was weak and febrile, with swelling and acute tenderness below the left eye. The left antrum was radiologically opaque. *Staphylococcus pyogenes* and *Escherichia coli* were grown from antral washings. By this time he had bilateral lumbar pain, varying with the height of fever. There were 2–4 parts per 1000 of protein in the urine. Blood-urea, 40 mg. per 100 ml. Specific-gravity range of urine, 1014–1004. Urea-clearance, 53–57 of normal. Intravenous pyelogram normal.

Bed rest was followed by improvement, but fever and antral pain recurred with epistaxis in August, 1956. Ankle œdema appeared, the liver and spleen became palpable, and bilateral fluffy exudates and one hæmorrhage developed in the fundi oculi. Blood-pressure (B.P.) 150/90 mm. Hg, hæmoglobin (Hb) 88%, white-cell counts 5000 per c.mm. with a normal differential, erythrocyte-sedimentation rate (E.S.R.) 46 mm. in the first hour. Blood-culture sterile. Wassermann reaction (W.R.) negative. Total serum-protein 5.8 g. per 100 ml. (albumin 3.2 g.), with a rise in both alpha-globulins on electrophoresis.

Tetracycline treatment produced no change in signs. Inferior-turbinate biopsy showed non-specific histiocytic granulation tissue, with small areas of necrosis. No giant cells or vasculitis were seen.

A Caldwell-Luc operation was performed in November, 1956. Proteinuria continued and increased to 8 parts per 1000. Renal biopsy showed interstitial fibrosis with dilated tubules filled with protein-like "colloid" material; there was no evidence of a definite glomerular abnormality, and there were no granulomatous or vascular changes.

His deterioration was steady, unaffected by treatment with cortisone 250 mg. daily, prednisone 80 mg. daily, or iodides 4.5 g. daily. In December, 1956, he had earache and some deafness on the left. An ulcer appeared on the left palate, perforating into the nose and spreading to the fauces. Local irradiation was of no benefit. His blood-urea rose to 147 mg. per 100 ml., and he died in uræmia in January, 1957. Necropsy not permitted.

Case 2.*—A woman clerk, aged 28, had a bilateral intranasal antrostomy in September, 1949, for chronic nasal obstruction. In mid-January, 1951, she felt ill and had severe left frontal headache. She did not improve with antral washouts; anorexia, vomiting, and drowsiness led to hospital admission on Feb. 27, 1951. Temperature 105°, pulse-rate 130. The nasal septum was deviated to the left. There was a free watery discharge from the left nostril, and posteriorly pus was dripping into the hypopharynx. The left frontal and maxillary sinuses were tender.

Penicillin, streptomycin, and sulphadimidine produced no improvement. Left antral washouts yielded mucopus and blood-clots. On March 2, 1951, the liver was easily palpable, and so was the tip of the spleen. Swelling over the antrum increased despite the use of chloramphenicol and aureomycin. The temperature ranged between 99° and 104°F. Hb 92%, white cells 3200 (polymorphs 36%), E.S.R. 18 mm. in the first

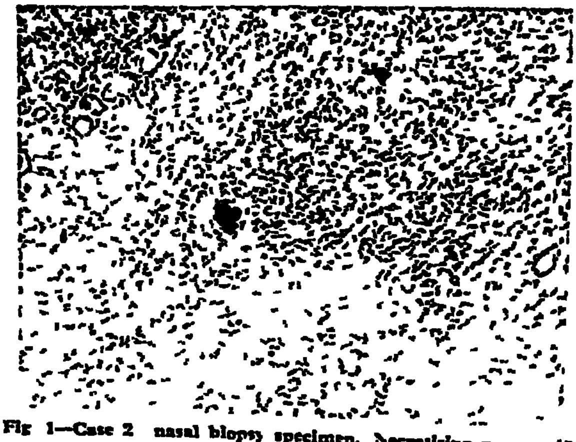

Fig. 1—Case 2: nasal biopsy specimen. Necrotising non-specific inflammatory reaction. (× 60.)

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* Briefly reported by Mr. F. W. Watkyn-Thomas in the *Medical Annual*, 1952, p. 242.

hour, flocculation tests negative Prothrombin concentration 56% Sternal marrow normal Urine contained 2 parts per 1000 of protein and many granular casts Blood-urea 18 mg per 100 ml W R negative Blood-culture sterile

A 10-day course of corticotrophin made her no better A wide exploratory operation was carried out on April 4, 1951 Necrotic tissue extended into the antrum and the ethmoid and sphenoid air cells Histological examination showed a non-specific granuloma with large areas of necrosis The palate ulcerated through into the antrum She died on May 22, 1951, after a violent epistaxis from the left nostril

Post mortem the local lesion showed no evidence of giant cells or vascular changes (fig 1) The liver weighed 1310 g and the spleen 235 g, no systemic lesions were demonstrated in them or any other organ

Case 3—An hotel night porter, then aged 22, had an abscess below his right ear drained in July, 1947 A year later he noticed enlarged glands in the right posterior triangle of the neck White-cell count and chest radiograph were normal, and the glands subsided on penicillin treatment In October, 1948, a swelling in the left nostril appeared and became larger despite penicillin treatment Biopsy showed pleomorphic highly cellular granulation tissue with incipient necrosis but no vascular changes

He was admitted to hospital in January, 1949, by which time his left nostril was obstructed by a large crust-covered ulcer involving the left turbinate bone and extending into the vestibule of the nose He was febrile and ill Hæmoglobin 88%, W R and Kahn negative, sternal marrow normal Weak positive colloidal-red and cephalin-cholesterol tests Chopra and formol-gel tests negative Blood-culture sterile

In mid-February a crop of subcutaneous nodules, raising and attached to the skin, appeared on the front of the chest Temperature remained between 101° and 103°F Urine contained 0 8 parts per 1000 of protein Blood-urea 90 mg per 100 ml

On March 6, 1949, he became stuporous, jaundiced, and incontinent Serum-bilirubin 6 mg per 100 ml He died 3 days later Neither local lesion nor general condition were influenced by sulphonamide, penicillin, streptomycin, or neoarsphenamine

Post mortem there was no systematised vasculitis, but there were non-specific granulomatous inflammatory changes in the epididymis and the subcutaneous fat and the corium of the skin In the liver there was centrilobular necrosis due to congestion No other abnormalities were found

Case 4—A housewife, aged 25, developed acute right maxillary sinusitis, with bloody nasal discharge, in February, 1954 She had a temperature of 99 6 F and radiographs showed an opaque right antrum Culture of antral washing yielded *Streptococcus viridans* and pneumococci There was no albuminuria

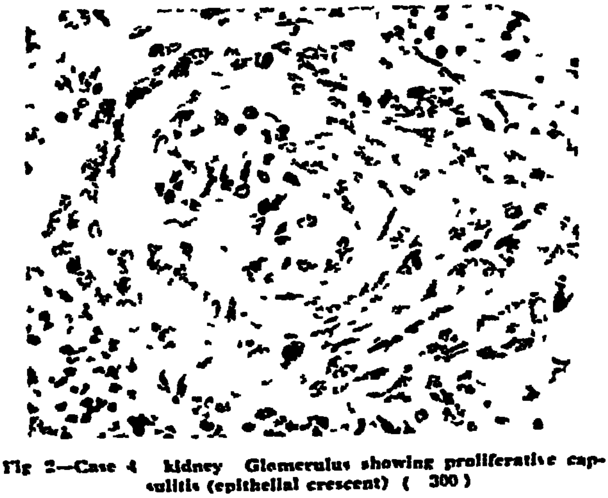

Fig 2—Case 4 kidney Glomerulus showing proliferative capsulitis (epithelial crescent) (× 300)

Nasal discharge continued, and granulation tissue formed on both sides of the nasal septum Biopsy of this showed non-specific inflammatory tissue without necrosis and without giant cells

In April, 1954, she became deaf and developed otorrhœa with an anterior perforation of the right eardrum Despite penicillin treatment the nasal cartilage quietly collapsed producing a saddle nose in May A profuse epistaxis brought her into hospital

She was anæmic and had a macular rash on the extensor aspects of elbows and knees Her blood-pressure was 150/90 and she had slight œdema of the ankles Hæmoglobin 47% White cells 21,200 per c mm (91% polymorphs), E S R 120 mm in the first hour Blood-culture sterile W R and Kahn negative The urine contained protein 2–4 parts per 1000 and also many erythrocytes and occasional granular casts Blood-urea 110 mg per 100 ml Chest radiograph two rounded opacities in the left midzone and some basal congestion She became oliguric, and died in uræmia with a blood-urea of 225 mg per 100 ml

The postmortem findings (Dr D H Haler) included a necrotising vasculitis in the kidneys and spleen, with a widespread proliferative capsulitis (crescent formation) of the renal glomeruli (fig 2) The association of these changes with a nasal granuloma is characteristic of Wegener's granulomatosis, according to Godman and Churg (1954), the essential features of Wegener's granulomatosis are (1) a necrotising granuloma of the respiratory tract, (2) generalised vasculitis, and (3) glomerulonephritis—all of which were present in this case

Discussion

All these cases showed progressive destructive lesions in the nose or paranasal sinuses, without demonstrable bacterial or neoplastic cause All patients had intermittent fever, and systemic involvement was suggested clinically by hepatomegaly (two cases), splenomegaly (two), lymphadenopathy (two), subcutaneous nodules (one), retinitis (one) (cf Lindsay et al 1944, Williams 1949 (case 1), Howells 1955 (case 2)), and epididymitis (one), (cf Fahey et al 1954 (case 3)) All the patients also had albuminuria, though this was transitory in one, and three had terminal azotæmia, though none developed hypertension Radiographs suggested lung lesions too in one case Two patients appeared to die from renal failure, one from hæmorrhage, and one from toxæmia

These cases, we suggest, form an arc extending from the local lesions to the full recognisable picture of Wegener's granulomatosis Cases 1 and 2 had characteristic local lesions of "malignant granuloma of the nose" There was strong clinical suggestion of systemic involvement, though this was not demonstrated histologically Case 3 had again local lesions characteristic of this type The systemic lesions histologically were non-specific and no definite arteritis was seen Case 4 had the so-called Wegener's granulomatosis with arteritis

We have been impressed by the consistent shape of the illness, which has three stages

1 A minor rhinological lesion (usually nasal obstruction), with serosanguinous discharge or sinusitis, commonly *followed* by operation At this stage there is no indication of the future course of the disease

2 The development of a local destructive granuloma

3 The late appearance of systemic lesions

The patient may die at stage 2 from local complications, or at stage 3 from either local or systemic effects—commonly renal failure

Though the ætiology of the condition is at present unknown, Watkyn-Thomas (1952) speaks of "a general belief that hypersensitivity either to a toxin or an organism must play some part in the disease as we see it in the nose" Williams (1949) and Godman and Churg (1954) also emphasise the role of hypersensitivity We, too, think that a hypersensitivity reaction of some sort is the most probable explanation of the systemic lesions Hypersensitivity is known to be associated with granulomatous lesions (Goddard 1947), vasculitis, and renal damage—both when it is induced experimentally (Zeek et al 1948, Rich et al 1943) and when it occurs in man in such diseases as polyarteritis nodosa (Klinge 1933, Klemperer 1942, Teilum 1946)

Neither antibiotics nor steroids seem to have produced more than short-lived temporary improvement in those patients who have died from the effects of the local lesion X-ray therapy does, however, seem to have been definitely beneficial in some cases (Glass 1955, Howells 1955), and Ellis (1955) writes enthusiastically of its use Hultberg et al (1957), in the light of their experience of ten cases, recommend the use of combined steroid hormones and X rays in the treatment of the local granuloma

If further experience shows that radiotherapy is capable of halting the local lesions, it becomes even more important to prevent the development of systemic lesions No treatment so far reported has been of any value once they have appeared If they are due to hypersensitivity reaction, then the use of antibiotics can be of no value and may even be provocative Steroid treatment, on the other hand, would be rational Williams (1952), reviewing the use of steroids in otolaryngorhinology, remarks that they offer a chance of saving the life of a patient suffering from malignant granuloma Their use has so far proved disappointing, but this may well be because they have been given too late

In our view, if a patient develops malignant granuloma, treatment with full doses of steroids should be started at once This could be combined with local radiotherapy It seems that only a combination of irradiation and adequate cortisone therapy may yield better results Antibiotics should be avoided This is how we shall treat the next case we see, and we make the suggestion now, for it will probably be many years before we have the opportunity ourselves of observing its value

Summary

Four fatal cases of malignant granuloma of the nose are described Three of these had systemic involvement

Steroid hormones may have a place in treatment

Our thanks are due to Mr F W Watkyn-Thomas, Miss J Wadge, and Prof M L Rosenheim for permission to use case-records

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EFFECT OF CHLOROTHIAZIDE ON THE HYPOTENSIVE ACTION OF MECAMYLAMINE AND ON ITS URINARY EXCRETION

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It has been reported that chlorothiazide potentiates the action of hypotensive drugs (Freis and Wilson 1957, Hollander and Wilkins 1957, Tapia et al 1957) This finding is described in the case of hypotensive agents with widely varying modes of action, including ganglion-blocking drugs (such as mecamylamine, pentolinium, and chlorisondamine) and also veratrum alkaloids, reserpine, and hydrallazine Chlorothiazide is effective in increasing urinary sodium excretion, and sodium depletion is known to enhance the effect of ganglion-blocking agents (Smirk and Alstad 1951) It is reasonable to suggest, therefore, that the potentiating effect of chlorothiazide is due to its action in causing a sodium diuresis

Chlorothiazide is also a powerful carbonic-anhydrase inhibitor in vitro In vivo, Ford et al (1957) have shown that an increased excretion of bicarbonate and a rise in urinary pH follow the administration of the drug The excretion of mecamylamine is increased in the presence of an acid, and decreased in the presence of an alkaline urine (Baer et al 1956), and acetazolamide, the diuretic effect of which is due entirely to its action as a carbonic-anhydrase inhibitor, causes retention of mecamylamine in the body, thus increasing the hypotensive effect (Milne et al 1957) The similar carbonic-anhydrase inhibiting property of chlorothiazide suggests that this drug might also promote the retention of mecamylamine—a hypothesis which is supported by the following observations

Observations

An increased hypotensive action was noted when chlorothiazide was given to an outpatient who was already receiving mecamylamine

A man, aged 48, with severe benign hypertension, whose blood-pressure was difficult to control despite a total daily dose of 50 mg of mecamylamine, was given chlorothiazide in addition (0 5 g twice daily) After the first dose he noticed an increase in the weakness which had been a complaint ever since he had been taking mecamylamine, together with severe dryness of the mouth and increased blurring of vision The patient spontaneously described his symptoms as an "amplification" of the familiar effects of mecamylamine When he was next seen, a week after chlorothiazide had been started, his blood-pressure was 145 95 mm Hg (standing up), compared with the readings of 190 120–250 150 recorded during the previous twelve months, and this effect has been

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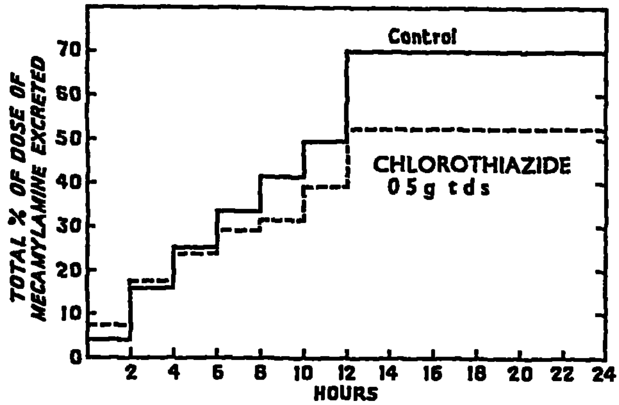

Fig 1—Urinary excretion of mecamylamine after an oral dose of 10 mg

maintained by continuing chlorothiazide, though on a smaller dose (0 25 g daily) which makes the regime more tolerable

Excretion of mecamylamine in the urine was measured in three inpatients

(1) In a woman aged 52, with benign hypertension and normal renal function, the urinary excretion of mecamylamine after single oral doses of 10 mg was estimated before and during a period of treatment with chlorothiazide 0 5 g thrice daily (fig 1) The twenty-four-hour excretion of mecamylamine was significantly depressed while chlorothiazide was being administered

(2) Fig 2 shows observations made on a hypertensive patient aged 53, receiving 7 5 mg mecamylamine twice daily The addition of chlorothiazide 0 5 g thrice daily to his treatment was followed by a striking fall in blood-pressure, with severe postural hypotension, on the third day after chlorothiazide had been started he was complaining of weakness, blurring of vision, and dryness of the mouth, which had not troubled him previously, and mecamylamine had to be suspended The urinary excretion of mecamylamine was reduced to about a third of the previous level when chlorothiazide was added (fig 2)

(3) In a man, aged 57, with type-II nephritis and hypertension, the effect of chlorothiazide on urinary mecamylamine excretion is shown in the accompanying table In the first three days after chlorothiazide was started the excretion of mecamylamine dropped by 30%, and this fall was most evident during the first day on chlorothiazide At the same time the patient complained of dryness of the mouth, and a further fall in blood-pressure was recorded

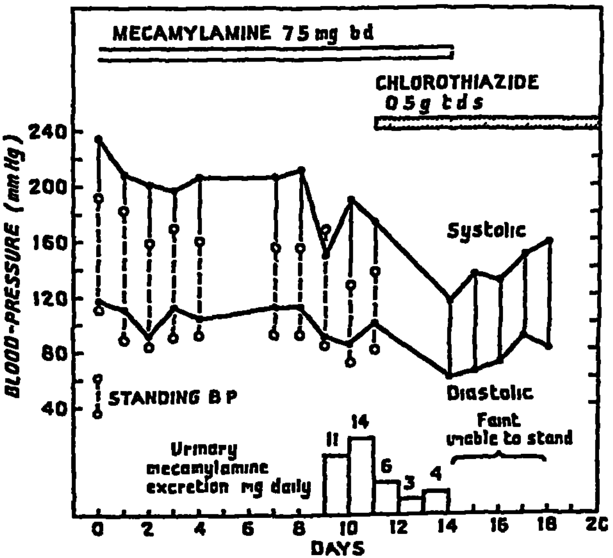

Fig 2—Effect of addition of chlorothiazide to mecamylamine on the blood-pressure and urinary mecamylamine excretion

Discussion

From these observations it is clear that the urinary excretion of mecamylamine is depressed by chlorothiazide It is likely that this effect is due to the increase in urinary pH which follows administration of the latter drug The consequent retention of mecamylamine in the body must contribute to the increase in hypotension when chlorothiazide is given to a patient receiving mecamylamine, and this is borne out by the simultaneous increase in side-effects from ganglionic blockade noted in our patients Mecamylamine retention was most pronounced on the first day of administration of chlorothiazide (see table) By the third day excretion had once again come into balance with the administered dose As the hypotensive action and side-effects were still pronounced it seems likely that concentrations within the body had been set at a higher level

If this were the only result of combining the two drugs, little would appear to be gained The claim, however, that chlorothiazide can potentiate the hypotensive effect of such chemically varied drugs as pentolinium, reserpine, and hydrallazine, as well as mecamylamine, might indicate an additional mode of action, perhaps related to depletion of body-sodium If such an additional effect is confirmed, this might play an important part when chlorothiazide is given together with another hypotensive agent over a long period

EFFECT OF CHLOROTHIAZIDE ON URINARY MECAMYLAMINE EXCRETION

Day	Mecamylamine (mg b d)	Chlorothiazide (g b d)	Mecamylamine excretion (% dose per 24 hr)	Mean excretion
1	15	0	83	79%
2	15	0	70	
3	15	0	83	
4	15	0 5	19	54%
5	15	0 5	59	
6	15	0 5	83	

It has been suggested (Hollander and Wilkins 1957) that chlorothiazide alone may have a hypotensive action in some patients in the absence of treatment with any other known hypotensive agents, and that this action is too rapid in its onset for it to be due solely to sodium depletion We have so far been unable to confirm this finding, in four patients who were given an intravenous injection of 0 5 g chlorothiazide, and whose blood-pressure was recorded for two to six hours after the injection, no change in the level of blood-pressure and no postural hypotension were observed, despite pronounced sodium diuresis (120 mEq in six hours in one case) Since an average of 90% of an intravenous dose of chlorothiazide is excreted in the urine within six hours (Beyer 1957, Milne 1958), this argues against any direct hypotensive action of the drug

Summary

Administration of chlorothiazide increases the hypotensive effect of mecamylamine

This effect is due at least partly to decreased elimination of mecamylamine from the body

We thank Prof J McMichael and Dr M D Milne for their help and advice, and Dr Milne for the chemical estimations

References at foot of next column

CHANGES IN SERUM-POTASSIUM LEVEL AND IN pH OF ARTERIAL BLOOD IN RESPIRATORY ACIDOSIS

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Emphasis has been placed on the occurrence of carbon-dioxide narcosis in emphysematous patients who develop acute respiratory infections and on the dangers of excessive oxygen therapy, but little attention has been paid to accompanying changes in the serum-electrolyte levels in these patients, though there have been several recent studies of electrolyte balance in respiratory acidosis and alkalosis induced experimentally

One of us (H P S F) observed severe hyperkalæmia in 2 emphysematous patients in respiratory failure as the result of acute respiratory infections and with gross mental disturbances and convulsive movements One of these patients had been receiving intermittent oxygen therapy through a face-mask for some days, the other showed a further rise in the serum-potassium level after he had been treated in an oxygen tent

This observation prompted us to make further studies of serum-electrolyte levels in similar patients and to attempt to correlate them with changes in the pH of arterial blood

Material and Methods

All the patients were men, aged 49 to 66 (mean 61), and had chronic bronchitis and emphysema They have been divided into three groups according to the method of study

Group 1 consists of the 2 above-mentioned patients in whom serial estimations of serum-electrolytes were made during their illness and severe hyperkalæmia was repeatedly observed

Group 2 consists of 6 patients in whom serum-electrolytes were estimated before and after prolonged administration of oxygen

Group 3 comprises 8 patients in whom the pH of arterial blood was recorded in parallel with the estimation of serum-electrolyte levels before, during, and after inhalation of oxygen

Results

Group 1 Serial Estimations of Serum-electrolytes

Case 1 —A man, aged 56, had had bronchitis for ten years and an acute exacerbation following a respiratory infection three days before admission

On admission to Lambeth Hospital on Feb 13, 1956, he had emphysema, bronchitis, and congestive cardiac failure His blood-pressure was 140/90 mm Hg Radiography of his chest showed emphysema and prominent pulmonary arteries but no consolidation. Electrocardiography showed right ventricular hypertrophy

Treatment and progress —The patient was treated with penicillin and ephedrine, and his condition gradually improved until three weeks after admission, when he became more breathless and cyanosed, with severe tachycardia and increased moist sounds at his lung bases Intermittent oxygen therapy was given through a face-mask, and he was digitalised and treated with mercurial diuretics A few days later he became disoriented and developed convulsions A random sample of venous blood at this stage showed serum-potassium 7 0 mEq per litre, sodium 125 mEq per litre, chlorides 78 mEq per litre, CO_2-combining power 28 mEq per litre, and urea 200 mg per 100 ml The patient was then placed in an oxygen tent and given 'Resonium A' in the dosage of 15 g t.d.s in an attempt to lower the serum-potassium level From this time his condition gradually improved, and the serum-potassium and blood-urea levels fell towards normal, but the potassium level tended to rise again subsequently (fig 1) The patient was transferred to a convalescent unit four and a half weeks after admission Some months later it was learnt that he had died in another hospital, but no details are known

Case 2 —A man, aged 64, had had winter bronchitis for three years and had become increasingly breathless for three weeks

On admission to Lambeth Hospital on March 26, 1956, he had emphysema and an acute exacerbation of chronic bronchitis but no congestive failure His blood-pressure was 145/80 mm Hg Electrocardiography showed tall P waves Radiography of his chest showed no consolidation on admission, but bronchopneumonia appeared later

Treatment and progress —The patient was given penicillin and streptomycin Forty-eight hours after admission he was placed in an oxygen tent, in which he developed convulsive movements and became mentally confused He complained of severe and continuous headaches and was found to have papillœdema The cyanosis was relieved when he was placed in the tent but recurred as soon as he was removed from it On the second day of treatment in the tent a random sample of

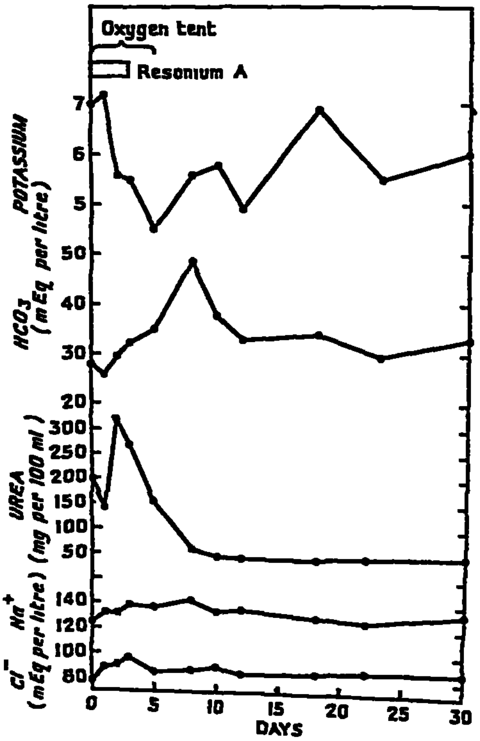

Fig 1—Blood-urea and serum-electrolytes in case 1

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venous blood showed a serum-potassium level of 6 4 mEq per litre, sodium 135 mEq per litre, chlorides 84 mEq per litre, CO_2-combining power 39 mEq per litre, and urea 36 mg per 100 ml Next day the serum-potassium level had risen to 8 8 mEq per litre During the next week, throughout which the patient was nursed in the oxygen tent, the serum-potassium levels and the CO_2-combining power fluctuated but tended to fall (fig 2) His mental state gradually returned to normal, and the convulsions subsided

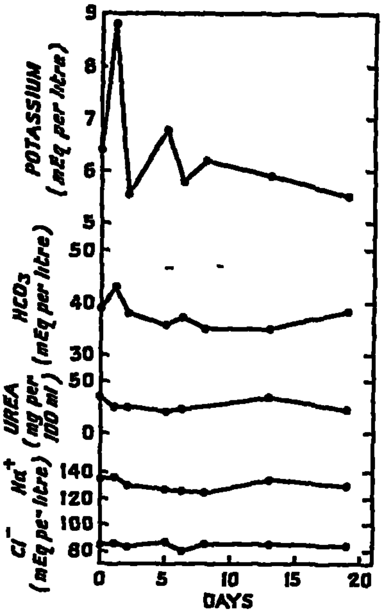

Fig 2—Blood-urea and serum-electrolytes in case 2

The blood-urea level remained normal throughout Twenty-three days after admission, when he had been out of the oxygen tent for twelve days, he had a sudden attack of dyspnœa and died within three-quarters of an hour

Necropsy findings—Mucopurulent bronchitis with early bronchopneumonia, severe emphysema, moderate right ventricular hypertrophy and dilation and congestion of the liver, spleen, kidneys, and brain were found

TABLE I—SERUM ELECTROLYTES OF PATIENTS IN GROUP 2

Case no	Age (yr)	Serum electrolytes (mEq per litre)					Blood-urea (mg per 100 ml)
			K	Na	Cl	HCO_3	
3	65	Before O_2	5 3	134	94	27 2	27
		After O_2	5 8	140	97	28 1	25
4	52	Before O_2	5 1	137	94	28 6	43
		After O_2	5 4	135	103	29 5	
5	64	Before O_2		139	95	31 1	40
		After O_2	5 9	142	98	33 9	43
6	60	Before O_2	4 8	142	99	33 5	30
		After O_2	5 0	146	102	33 9	34
7	64	Before O_2	4 2	137	96	29 0	34
		After O_2	4 2	129	101	29 9	35
8	65	Before O_2	4 3	137	99	24 0	22
		After O_2	4 4	137	96 5	24 5	20

Group 2 Serum-electrolytes Before and After Inhalation of Oxygen

In view of the sharp rise of the serum-potassium level which followed the use of an oxygen tent in case 2 the effects of prolonged administration of oxygen on the serum-electrolytes were studied in emphysematous patients

Oxygen was given through a face-mask for three hours to each of 6 patients with chronic bronchitis and emphysema, all of whom also had pulmonary tuberculosis Samples of venous blood were taken immediately before and after this period

The results (table I) reveal a slight but probably significant rise in serum-potassium level in 1 of the patients and a rise of doubtful significance in 1 other 1 other patient had significant hyperkalæmia at the end of the oxygen inhalation, but unfortunately the initial potassium reading was spoilt

Group 3 Arterial Blood pH and Serum-electrolyte Levels Before and During Inhalation of Oxygen (table II)

Observations were made on 8 patients with chronic bronchitis and emphysema who had been admitted as emergencies to St Bartholomew's Hospital, in most cases within the previous twenty-four hours, with acute respiratory infections These patients were similar to those in group 1 but are considered separately because they were studied in different ways

Of the 8 patients 5 had clinical evidence of congestive heart-failure, and 4 of 7 patients had electrocardiographic evidence of right ventricular hypertrophy Of the 8 patients 5 died within the next few days or weeks The cause of death was respiratory failure in 3 cases (in 1 of them a spontaneous pneumothorax contributed to death), bronchopneumonia in 1 case, and cardiac infarction complicated by auricular flutter and heart-failure in 1 case

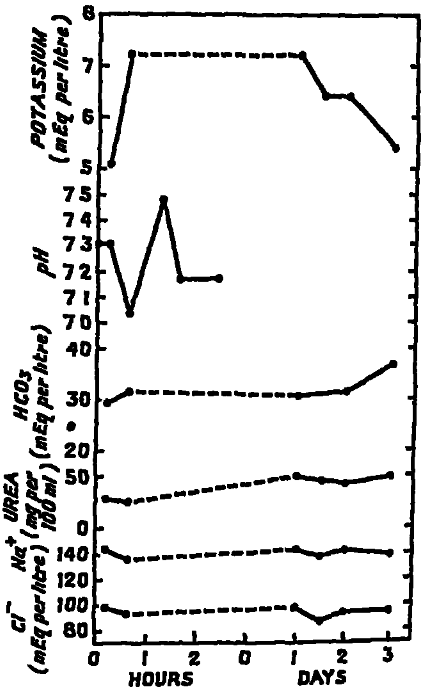

Fig 3—Blood-urea, serum-electrolytes, and pH of arterial blood in case 9

Oxygen therapy was deliberately withheld for periods of up to three hours before the observations of arterial blood pH and serum-electrolytes were started

Measurement of pH of Arterial Blood

Samples of blood were withdrawn through an indwelling Riley needle placed in the brachial artery

The pH was measured at 37 5°C at the bedside with the apparatus described by Mendel (1957) The accuracy of the measurement was ± 0 02 of a pH unit

TABLE II—GROUP 3

Case no	Age (yr)	Right ventricular hypertrophy		Congestive failure	Serum electrolytes (mEq per litre)				Blood urea (mg per 100 ml)	Arterial blood	
		E.C.G	Necropsy		Na	K	Cl	HCO_3		pH	pCO_2 (mm Hg)
9	54	+	+	+	139–143 5	5 1–7 2	87 5–99 2	29 5–37 0	21–50	7 31–7 05	
10	55	+		+	131–141	4 4–5 9	84–91	30–41	30–49	7 00–7 59	
11	60		+	+	134–139	6 1–4 4	89–92	29–32	23–41	7 57–7 25	
12	61	+	0	0	134	4 0–5 4	89–92	29–32	66–71	7 49	
13	66	0			125 137	3 6–5 2	62–91	28–35	50	7 30–7 15	57–75
14	66	+		0	140–142	4 6–5 0	100–101	27 6–27 8	44–46	7 42–7 27	47
15	65	0		+	130–143	4 2–4 3	96 5–102 5	20 6–22 0	67	7 45–7 31	
16	49	0		0	133–139	4 4–4 9				7 32–7 25	55–66

The pH of five or more samples from each patient was determined. The first two samples were taken before oxygen was administered. The others were withdrawn at various intervals during the inhalation of oxygen, the precise times of sampling were not fixed. Exact determinations of pH were made when rough estimates indicated that changes were taking place.

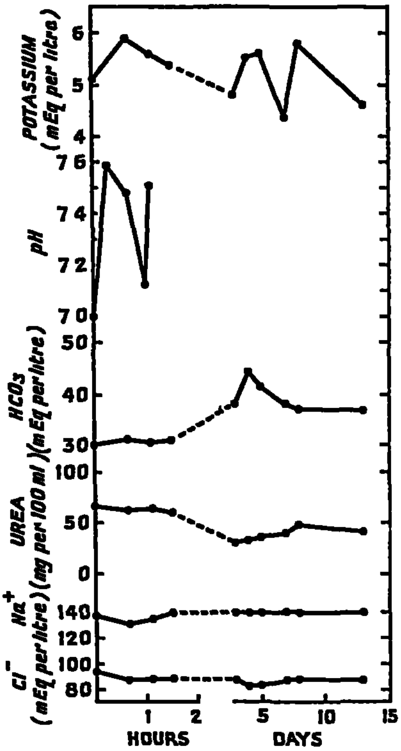

Fig. 4—Blood-urea, serum-electrolytes and pH of arterial blood in case 10.

Arterial puncture was found to provoke slight hyperventilation in the first 5 patients studied, this in itself produced an initial change in pH. In the 3 remaining patients ventilation was therefore measured also.

The resting pH was in the low normal range (mean value 7·39) in 7 of the 8 patients, once the initial effect of hyperventilation had worn off. After oxygen breathing was started, the pH decreased (mean decrease 0·15 pH unit in a mean time of fifty-six minutes) and it was still decreasing in 3 of 5 patients when the oxygen was withdrawn. The most rapid decrease observed was from 7·31 to 7·05 in twenty-two minutes in case 9 (table II and fig. 3). Case 10 showed the opposite effect: he was clearly hyperventilating throughout the period of oxygen breathing, and the pH of his blood increased steadily (table II and fig. 4).

The minute ventilation began to diminish about ten minutes after the inhalation of oxygen was started in the 3 patients in whom it was measured. After oxygen had been inhaled for an hour, the minute volume of ventilation had fallen to about 60% of the resting level in each patient—e.g., case 16 (table II and fig. 5).

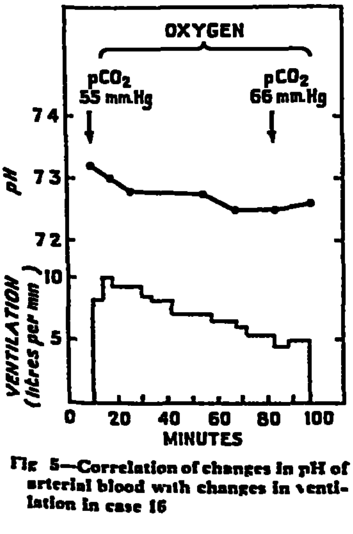

Fig. 5—Correlation of changes in pH of arterial blood with changes in ventilation in case 16.

Measurement of the urinary pH in 2 patients revealed that the acidæmia was associated with increased acidity of the urine.

Electrolyte Estimations

Arterial samples were also taken for serum-electrolyte estimations both before inhalation of oxygen and at intervals during inhalation. Samples were taken particularly when considerable changes had taken place in the pH of the arterial blood.

In all the cases serum-sodium and serum-potassium were estimated by flame photometry, care being taken to avoid hæmolysis of the samples. In 4 cases specimens of urine were collected immediately before and after the inhalation of oxygen, and each subsequent specimen passed during the first twenty-four hours was also saved, thereafter consecutive 24-hour specimens of urine were saved for a few days. In each of the specimens of urine passed during the first twenty-four hours and each of the 24-hour collections the levels of sodium, potassium, and chloride were estimated.

The initial serum-potassium level was significantly raised in only 1 of the 8 cases. In this case the serum-potassium level was 6·1 mEq. per litre and the blood-urea level 41 mg. per 100 ml., both of these values being obtained on admission. The serum-potassium level had fallen to 4·4 mEq. per litre and the blood-urea level to 23 mg. per 100 ml. next day, when the studies of arterial blood pH and oxygen inhalation were made.

Of the 7 other patients with initially normal serum-potassium levels 2 showed a significant rise in level during the inhalation of oxygen. In 1 of these the level rose from 5·1 to 7·2 mEq. per litre after forty minutes, with a corresponding decrease in arterial pH from 7·31 to 7·05, and fell towards the resting level only after three days, during which intermittent oxygen therapy was continued (fig. 3). The blood-urea level was normal on the first day of study but subsequently rose. In 1 other patient the serum-potassium level rose from 5·1 to 5·9 mEq. per litre after inhalation of oxygen for forty minutes but subsequently fell again towards the resting level during the next fifty minutes in spite of the continued administration of oxygen. This was the patient in whom the pH increased during oxygen therapy instead of decreasing. The blood-urea level rose to 60–68 mg. per 100 ml. at this time (fig. 4).

None of the 6 other patients showed significant changes in serum-potassium levels during or after the administration of oxygen. Raised serum-potassium levels were confined to the most seriously ill patients with mental changes. None of the 8 patients initially showed a CO_2-combining power in excess of 32 mEq. per litre, in 4 patients the initial value was 28–32 mEq. per litre. The initial serum-chloride level was 89–100 (mean 94) mEq. per litre (table II). In none of the patients did these levels or the serum-sodium levels show any definite trends on serial estimation, except in 2 patients in whom the CO_2-combining power increased considerably during the first few days; these were the 2 patients who showed sharp rises in serum-potassium levels during inhalation of oxygen, but the increase in CO_2-combining power took place at the stage when the serum-potassium levels were falling again (cases 9 and 10, figs. 3 and 4). Unfortunately samples of urine were not collected from these 2 patients. None of the other patients showed any significant trends in the excretion of electrolytes, in particular there was no obvious retention of potassium.

Discussion

Carbon Dioxide Retention

The mechanism of carbon-dioxide narcosis in emphysematous patients and the accompanying rise of pCO_2 and decrease of pH in the arterial blood, as well as the exacerbation of these changes which may result from excessive oxygen therapy, have been fully discussed by other workers (Taquini et al. 1948, Donald 1949, 1953, Comroe et al. 1950, Motley 1950, Hickam et al. 1952, Westlake et al. 1955, Sieker and Hickam 1956, Simpson 1957, and others). All agree that excessive administration of oxygen in emphysematous patients may lead to diminished ventilation, inadequate elimination of carbon dioxide by the lungs, retention of carbon dioxide in the blood, and acidæmia.

The pH of the arterial blood decreased with surprising rapidity in our patients and was still decreasing after three hours' administration of oxygen.

A ventilatory deficit of as little as 1 litre per minute may cause the retention of as much as 2 mEq. of carbon dioxide a minute That the pH of the blood does not decrease more profoundly still is due to the buffer capacity of the blood and the tissues

A compensatory rise in the blood-bicarbonate level may take place in respiratory acidosis Dorman et al (1954) have shown that inhalation of a mixture of carbon dioxide and oxygen leads to a rise in the pCO$_2$ and a decrease in pH in the blood in dogs, and that this is promptly followed by an increased reabsorption of bicarbonate-bound base by the renal tubules, the degree of reabsorption is related to the arterial pCO$_2$ They suggest that raised pCO$_2$ speeds up the hydration of carbon dioxide to carbonic acid by carbonic anhydrase in the tubular cells, and that this increases the available supply of hydrogen ions, which are in turn exchanged for base bound by bicarbonate in the tubular urine The serum-bicarbonate level rose significantly only in the most severely ill patients in our series (cases 1, 2, 9, 10, and 13) In 3 of these 5 patients the bicarbonate response was delayed for a few days after the start of oxygen therapy and was preceded by a rise in serum-potassium level (figs 1, 3, and 4) The 4th patient (case 2) had already had intensive oxygen therapy for twenty-four hours before chemical estimations were made, and both the serum-bicarbonate and the serum-potassium levels were raised by that time Cohn et al (1954) likewise observed that secondary changes in whole-blood buffer base were slow to develop in respiratory acidosis

Potassium

Hyperkalæmia appears to develop only occasionally, mainly in the most severe cases with carbon-dioxide narcosis There are several possible explanations of hyperkalæmia in these patients and of the tendency of the serum-potassium level to rise during the administration of oxygen

Hyperkalæmia in general may result from an increase in total body-potassium, as in renal failure and in adrenal insufficiency, or it may be due to transfer of potassium from the cells to the extracellular fluid, which may result from anoxia, from dehydration, or from deglycogenation of the liver after the release of adrenaline Excess extracellular potassium due to transfer from cells is normally eliminated through the kidneys, and persistent excess usually indicates impaired renal function (Elkinton and Danowski 1955) None of our patients showed evidence of adrenal insufficiency Urea was not invariably retained in the patients who had hyperkalæmia, nor did the serum-potassium levels always change in parallel with the blood-urea levels In case 1 hyperkalæmia was initially observed in the presence of severe retention of urea, but it persisted and even tended to increase again after the blood-urea had returned almost to normal All 3 patients with hyperkalæmia in group 3 had retention of urea at the same time or soon afterwards, but in 2 of them the serum-potassium level rose within forty minutes of inhalation of oxygen, the initial levels being not significantly raised In case 2 the serum-potassium level reached the highest value in the whole series despite persistently normal blood-urea levels The speed at which the level rose in the 2 patients in group 3 during the administration of oxygen is more in keeping with a transfer of potassium from the cells to the extracellular fluid than with renal retention of potassium, but it is possible that both mechanisms may come into play

Few clinical observations of this kind appear to have been published

Lovejoy et al (1954) reported serum-potassium levels of 6 0 and 5 45 mEq per litre in 2 patients with respiratory failure associated with acidosis and retention of carbon dioxide Both these patients developed narcosis during continuous oxygen therapy, and their serum-potassium levels rose to 7 1 and 6 4 mEq per litre The blood pH and the serum-potassium levels returned towards normal when the patients were treated with artificial positive-pressure respiration

Cherniack (1956) mentions a similar patient in whom the serum-potassium level was initially about 6 mEq per litre and fell to normal after positive-pressure respiration

Schwartz et al (1955) reported serum-potassium levels of 5 4–6 2 mEq per litre in 5 of 15 patients with cor pulmonale, in some of whom these levels tended to fall as the patients responded to acetazolamide

None of these workers comments on the serum-potassium levels, which are reported incidentally

Thomson (1957) has made detailed studies of changes in acid-base balance and serum-electrolyte levels in patients with bulbar poliomyelitis These patients developed carbon dioxide retention and acidosis When artificial respiration was applied, the pCO$_2$ decreased, the pH increased, the serum-potassium and serum-bicarbonate levels fell, and the serum-chloride level rose When respiratory obstruction occurred as the result of aspiration of secretions, the potassium levels rose to nearly twice the previous value The changes in extracellular potassium (the extracellular volume being estimated from the chloride space) were greater than could be explained by changes in extracellular volume or in renal excretion, and it was thought that they were due to transfers from cells

Experimental Studies in Animals and Man

Asphyxia in animals is associated with abrupt and striking rises in serum-potassium levels (D'Silva 1934) amounting to more than 40% in dogs (Dennis and Mullin 1938) and nearly 100% in cats (Cattell and Civin 1938) Inhalation of mixtures of carbon dioxide and oxygen also induces striking rises in serum-potassium levels in animals These changes do not entirely depend on renal mechanisms They are greater after ligation of the ureters and after nephrectomy but occur also when renal function is normal They are directly correlated with changes in the pH of the arterial blood and appear to result from transfer of potassium from the cells to the extracellular fluid in exchange for hydrogen ions, this being part of the tissue buffering mechanism in response to acidosis (Mackay 1947, Scribner and Burnell 1955, Scribner et al 1954, 1955, Giebisch et al 1955) Relatively small changes in serum-potassium levels have been reported in respiratory acidosis induced experimentally in man, but the concentrations of carbon dioxide inhaled have usually been lower than those applied to animals In experiments on man potassium ion appears to play a relatively insignificant role in the tissue buffer response (Elkinton et al 1953a and b, 1955) Usually the effects of respiratory alkalosis induced by hyperventilation in animals and in man are exactly the reverse of those occurring in acidosis potassium ion is transferred from the extracellular fluid to the cells and is excreted in the urine in increased amounts (Stanbury and Thomson 1952, Elkinton et al 1955, Giebisch et al 1955, Scribner and Burnell 1955) On the other hand, Hickam et al (1956) observed a mean rise in serum-potassium level from 4 0 to 5 2 mEq per litre following voluntary hyperventilation for about two minutes in healthy men The role of potassium ion in the regulation of acid-base balance has also been demonstrated in metabolic acidosis and alkalosis induced by the administration of such salts as ammonium chloride and sodium bicarbonate respectively Extracellular potassium levels increase in direct correlation with the decrease in pH in metabolic acidosis in animals, the potassium appears to be derived from the tissue cells, because there is no significant change in the potassium content of the red blood-cells The potassium changes are independent of the total body content of potassium, because they still take place when the body is depleted of potassium by the administration of deoxycortone acetate (Abrams et al 1951, Keating and Weichselbaum 1953, Burnell et al 1956) In man the serum-potassium level remains constant in metabolic acidosis induced by the ingestion of ammonium chloride, despite diminished absorption and increased excretion of the ion, indicating that potassium must have been transferred from the cells to the extracellular fluid (Sartorius et al 1949) Again, exactly the reverse changes were observed by the same workers in experimental metabolic alkalosis

The source of the excess extracellular potassium is not fully understood Keating and Weichselbaum (1953) found no evidence that it was derived from the red blood-cells in metabolic acidosis The potassium content of the isolated amphibian and rat diaphragm muscle in saline solution is reduced by increased carbon-dioxide tension (Fenn and Cobb 1935, Creese 1952, 1953), so perhaps the excess potassium is derived from the muscles Alternatively, it may be derived from the breakdown of glycogen in the liver under the influence of adrenaline

The rises in serum-potassium levels during the administration of oxygen in 2 of the patients in group 3 were correlated with sharp changes in the pH of the blood In case 9 (fig 3) the increase in pH was presumably due to an exacerbation of the already existing hypercapnia resulting from the removal of the anoxic stimulus to the respiratory centre In case 10 (fig 4) the pH increased rather than decreased, concurrently with the rise in serum-potassium level, and this increase in pH appeared to be due to hyperventilation This patient resembles the healthy people studied by Hickam et al (1956) in that the serum-potassium levels rose during hyperventilation Since the changes in serum-potassium levels took place inconstantly, it is doubtful whether they can be regarded as a direct effect of oxygen per se

An interesting parallel can be drawn from experiments on animals In the experiments already referred to, in which either asphyxia or acidosis was induced, the serum-potassium level rose higher as soon as the animals were returned to normal atmospheres (Cattell and Civin 1938, Scribner et al 1954, Young et al 1954) Signs of potassium intoxication usually did not appear during inhalation of carbon-dioxide mixtures in spite of the high serum-potassium levels (up to 14 mEq per litre), whereas electrocardiographic changes, ranging from bradycardia and prolongation of the QRS complex to ventricular fibrillation and cardiac arrest, developed soon after the animals were returned to room air (Scribner et al 1954, Young et al 1954) These experiments might suggest that acidosis protected the animals from potassium intoxication, but Young et al (1954) found that dogs in which high plasma-potassium levels had been induced by intravenous infusions of potassium chloride developed sudden and pronounced potassium intoxication when they were given inhalations of 30–40% carbon dioxide, before the plasma-potassium level rose higher

No direct evidence of toxic effects from the high serum-potassium levels was obtained in our patients, and it was impracticable to take serial electrocardiograms during the experimental period However, unexplained sudden death is known to take place in cor pulmonale (Brill 1939, Spain and Handler 1946, Simpson 1954), and sudden rises in extracellular potassium levels due to abrupt increases in pCO_2 might contribute to death in such cases If this were so, it would be a further reason for caution in applying oxygen therapy in respiratory acidosis

Summary

Serum-potassium levels higher than 5 5 mEq per litre were observed in 7 out of 16 patients with emphysema

Of these 7 patients 5 were acutely ill with respiratory infection In 3 of them serum-potassium levels of 7 mEq per litre or higher were recorded, these 3 were the most severely ill in this series and presented the clinical picture of carbon-dioxide narcosis

In 3 patients the serum-potassium levels rose rapidly during oxygen therapy In 1 of these the potassium change was associated with a rapid decrease of the pH of the arterial blood, another patient showed a slight rise in serum-potassium level in association with an increase of pH due to hyperventilation

The rise in serum-potassium level probably represents a transfer of potassium from the cells to the extracellular fluid This may be due to an increased pCO_2, and experimental evidence suggests that the potassium may be liberated from the muscles This is not the only mechanism, however, because the serum-potassium level may also rise slightly during hyperventilation Impaired renal function may also be a factor

Rapid rises of extracellular potassium concentration might contribute to the unexplained sudden deaths which occur in cor pulmonale The liability of such patients to develop carbon-dioxide narcosis as a result of intensive oxygen therapy is well recognised, and occasional hyperkalæmia developing under these conditions may be a further reason for caution in the administration of oxygen

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BLOOD COAGULATION BEFORE AND AFTER A FATTY MEAL

IN PATIENTS WITH CORONARY-ARTERY DISEASE AND IN HEALTHY CONTROLS

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A SHORTENING of the silicone clotting-time after a fatty meal in healthy people was reported by Fullerton et al (1953), Waldron and Duncan (1954), and O'Brien (1955) Other workers found no change (Tulloch et al 1953, Manning and Walford 1954, Merskey and Nossel 1957) There is, however, general agreement that the accelerated clotting-time of plasma in the presence of Russell's-viper venom (the 'Stypven' time) is shortened after a fatty meal An increase in postprandial coagulability of the blood might be part of the mechanism responsible for the alleged association between a high intake of dietary fat and coronary thrombosis If this hypothesis is correct, patients who have had coronary thrombosis might be expected to show a greater increase in coagulability after a fatty meal than do healthy people

Method

Twenty-one healthy men, aged 40–60, with no history of cardiac disease, acting as controls, and twenty-one male patients of similar ages who had had electrocardiographic and clinical evidence of coronary thrombosis between six months and several years previously but were otherwise healthy were investigated The controls were mostly volunteer blood donors and the rest out-patients at a physiotherapy department Each patient was usually, but not always, matched for age with the paired control, and the two groups were similar in social class, age, height, weight, and hæmoglobin levels

Usually two patients with two controls were seen each day at 9 A.M while fasting, and a sample of blood was collected by a two-syringe silicone technique They were then given a breakfast of tea and a little milk, toast and marmalade ad libitum and fat as indicated below Four hours later a second sample of blood was taken—the postprandial sample The fat content of the 'meal" was chosen to imitate in a controlled manner that of a normal breakfast This consisted of 20 g of butter, which alone would normally produce submaximal acceleration of the stypven time, and 5 g of 'Asolectin' (a commercial phospholipid extract of soya beans), which is about the quantity of phospholipid in two eggs To these two fats were added 20 g of coconut oil O'Brien (1957a) has shown that coconut oil produces no postprandial change in the stypven time of healthy people Patients with coronary disease might respond differently

After the first ten pairs of patients and controls had been investigated, the degree of postprandial change in the results of the coagulation tests were apparently the same in both groups and so might have indicated a maximal response in both groups The fat for the next eleven pairs was accordingly reduced to 15 g of butter, 2 g of phospholipid, and 15 g of coconut oil

The coagulation tests were as follows

(1) *Whole-blood clotting-time in silicone*—4 siliconised tubes in a water-bath at 37°C were each filled with 1 ml of blood, and the clotting-times were averaged

(2) *Whole-blood clotting-time in glass*—Glass tubes were used, the rest of the technique was similar to (1)

(3) *Whole-blood clotting-time with powdered glass*—50 mg of powdered silica glass was previously added to each of 2 tubes, the rest of the technique was similar to (1)

(4) *Stypven time of citrated blood*—To 0·1 ml of blood and 0·1 ml of Russell's-viper venom (stypven) 1:10,000 was added 0·1 ml of M/40 calcium chloride a minute later The test was repeated twice, and the clotting-times were averaged

(5) *Stypven time of plasma*—This was done as (4) but plasma obtained by centrifuging citrated blood (one part of 3·8% sodium citrate in water to 9 parts of blood) at 4000 r.p.m for 15 minutes was substituted for blood

(6) *Stypven time of dilute plasma*—Plasma diluted 1:4 with saline solution and stypven 1:100,000 were used

(7) *Heptane-stypven time*—0·1 ml of heptane was added to 0·1 ml of plasma and shaken, and the stypven test applied as for plasma Heptane and some other short-chain saturated hydrocarbons accelerate the stypven time of platelet-poor plasma This test has to be made soon after the addition of heptane, because the stypven time returns to normal when the heptane evaporates (A second addition of heptane has no effect) This acceleration of the stypven time may be due to heptane's rendering "available" some of the phospholipid bound to the plasma proteins (O'Brien 1958)

Results

A summary of the results is shown in table I These figures may be compared in different ways The patients' results may be compared with those of the controls as regards either the fasting figures or the postprandial figures Table II shows no significant difference between patients and controls either before or after the meal, but the fasting stypven time of dilute plasma nearly achieved significance In spite of this it was still theoretically possible that a difference between the groups would become manifest when the degree of change folllowing the meal—i e , the difference between the fasting and the postprandial figures—was used for the comparison This comparison is reported in the last two columns of table II, and again, with one exception, there was no significant difference between patients and controls

The one exception was the stypven clotting-time of dilute plasma which has a P value of slightly less than 1:20, the mean value for the controls was 18·1 seconds and that of the patients 13·8 seconds (table II) From a statistical point of view it was considered that this might be of no true significance, because it was to be expected that one or two tests would show a P value of this magnitude when so many tests were made

Since no difference is demonstrable between patients and controls, the two groups can be combined to study the effect of the meal on the various tests Table III therefore presents an analysis of all the results expressed as the degree of postprandial change The clotting-time in silicone-coated tubes and in glass showed a postprandial acceleration significant at a 5% level of probability, and the clotting-time with powdered glass and all the rest of the tests showed a highly significant degree of change All the coagulation times were shortened By inspection it could be seen that the stypven times of blood, of plasma, and of dilute plasma all altered closely in parallel The correlation between the fasting blood stypven time and dilute plasma, for example, was -0·75, which is highly significant There was no significant difference between the results of the first

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TABLE I—RESULTS

Test	Unit	Fasting						Postprandial					
		Patients			Controls			Patients			Controls		
		No	Mean	S D	No	Mean	S D	No	Mean	S D	No	Mean	S D
Clotting-time													
Powdered glass	Minutes	21	2.38	0.32	21	2.37	0.27	21	2.24	0.21	20	2.21	0.19
Glass	Minutes	21	7.87	0.97	21	8.03	0.97	22	7.56	1.29	20	7.77	1.25
Silicone	Minutes	21	18.08	3.02	21	19.27	2.74	21	17.17	2.59	20	18.46	1.68
Stypven (blood)	Seconds	22	14.9	3.23	20	15.4	3.44	22	10.6	1.69	19	11.4	2.79
Stypven (dilute plasma)	Seconds	22	42.0	10.83	21	50.0	16.30	22	28.2	8.65	20	31.9	11.24
Stypven (plasma)	Seconds	22	15.6	2.88	21	16.6	4.02	22	11.2	1.75	20	12.2	3.46
Heptane stypven	Seconds	22	10.7	1.19	21	11.1	2.16	21	9.7	0.74	20	9.8	1.03

ten pairs, who ate 45 g of lipids, and the remaining eleven pairs, who ate 32 g

Discussion

Comparison of Pre- and Post-prandial Results

The difference in the degree of significance between the postprandial shortening of the silicone clotting-time (5% level) and of the clotting-time in the presence of powdered glass (1% level) is fully explained if this shortening is due to "available active" phospholipids and if phospholipids are involved at an intermediate stage in in-vitro blood coagulation The long silicone clotting-time is much influenced by the slow initial stages of coagulation, involving, presumably, the Hageman factor (Ratnoff and Colopy 1955), antihæmophilic globulin, and Christmas factor, and the liberation of platelet-lipoid from the intact platelets The silicone clotting-time is therefore highly sensitive to minute variations in technique which affect these initial stages of coagulation, and any real alteration at a later stage would be partly obscured By adding an excess of the "contact factor"—powdered glass—these early stages are greatly accelerated and, in a sense, bypassed Subsequent stages would then become relatively more important, and any effect due to phospholipid would become more obvious

TABLE III—COMPARISON OF FASTING AND POSTPRANDIAL FIGURES (EXPRESSED AS DEGREE OF CHANGE) PATIENTS AND CONTROLS TOGETHER

Test	Unit	No of persons	Mean change (lipæmic-fasting)	Standard deviation	Significance
Clotting time					
Powdered glass	Minutes	41	− 0.17	0.33	0.01 > P > 0.001**
Glass	Minutes	11	− 0.33	0.95	0.05 > P > 0.02*
Silicone	Minutes	41	− 0.87	2.23	0.02 > P > 0.01*
Stypven (blood)	Seconds	41	− 4.1	2.17	P < 0.001**
Stypven (plasma)	Seconds	42	− 4.4	2.18	P < 0.001**
Stypven (dilute plasma)	Seconds	42	−15.8	8.39	P < 0.001**
Heptane stypven	Seconds	41	− 1.1	1.35	P < 0.001**

* Significant
** Highly significant } according to commonly accepted conventions

The stypven times of blood, plasma, and dilute stypven gave, as usual, highly reproducible results in contrast to the variation found between the four tubes used in the more orthodox clotting-tests All the stypven tests varied closely in parallel with each other and were obviously measuring the same phenomena In almost all the 42 results the stypven times showed much shortening, whereas the scatter of the more orthodox tests was much wider, some showing lengthening The highly significant postprandial acceleration of the heptane-stypven time must be interpreted with caution because this acceleration may well have been due to the same cause operating as in the other stypven tests but with an additional uniform degree of acceleration due to heptane superimposed on both the fasting and lipæmic times

TABLE IV—DILUTE STYPVEN TIME (SECONDS)

—	Patients	Controls
Mean fasting-time	42.0	50.0
Mean postprandial time	28.2	31.9
Mean degree of change	13.8	18.1

Comparison of Patients and Controls

Fasting—The near-significant difference between the fasting stypven time of the patients compared with the controls agrees well with McDonald and Edgill (1957), who found a small but significant difference in the fasting stypven times for one set of patients with coronary disease compared with healthy controls and none in a second set

Postprandially—It has already been mentioned that, with one exception, there was no significant difference between the two groups in the degree of postprandial change the difference between the patients and the controls in the dilute stypven test just achieved a significant value It has been suggested that this does not necessarily indicate a true difference However, this observation cannot be completely ignored, because this is the most sensitive of all the stypven tests—the degree of postprandial change was proportionally greatest with this test—and this same test also came near to showing a significant difference between patients and controls in the fasting samples

Conclusions

Coronary thrombosis may be due to an episodic thrombotic diathesis, in which case this series of tests

TABLE II—COMPARISON OF PATIENTS AND CONTROLS

Test	Unit	Patients v controls absolute figures (P—C)				Patients v controls degree of postprandial change (P—C)	
		Fasting		Postprandial			
		Difference of Means	Significance of difference	Difference of Means	Significance of difference	Difference of means	Significance of difference
Clotting-time							
Powdered glass	Minutes	0.01	P 0.90	0.03	0.70 > P > 0.60	−0.07	0.60 > P > 0.50
Glass	Minutes	0.16	0.70 > P > 0.60	−0.21	0.70 > P > 0.60	−0.10	0.80 > P > 0.70
Silicone	Minutes	1.19	0.20 > P > 0.10	−1.29	0.10 > P > 0.05	−0.13	0.90 > P > 0.80
Stypven (blood)	Seconds	0.5	0.70 > P > 0.60	−0.8	0.30 > P > 0.20	−0.4	0.60 > P > 0.50
Stypven (dilute plasma)	Seconds	8.0	0.10 > P > 0.05	−3.7	0.30 > P > 0.20	−3.9	0.20 > P > 0.10
Stypven (plasma)	Seconds	1.0	0.40 > P > 0.30	−1.0	0.30 > P > 0.20	−0.1	0.90 > P > 0.80
Heptane stypven	Seconds	0.4	0.50 > P > 0.40	−0.1	P > 0.90	0.2	0.70 > P > 0.60

would presumably not distinguish between the patients and the controls But the frequent finding of a familial history, and the repeated thromboses in some patients, suggest that certain people have a predilection to thrombosis—a permanent thrombotic diathesis The twenty-one healthy controls may have included one or more men who will have a coronary thrombosis, but in general the two groups were sharply divided the patients had clinical evidence of coronary thrombosis, and the controls had not The ideal test related to and measuring this thrombotic diathesis would also give a clearcut difference between patients and controls None of the tests reported here even remotely indicates such a difference The difference between patients and controls in some stypven clotting-tests which barely achieved significance is in line with, and possibly related to, the minor differences and the great overlap between the two groups when the β-lipoproteins are studied Clearly both these observations must be far removed from the immediate precipitating cause of a thrombosis in the coronary artery

From these investigations it might be concluded that there is no appreciable difference between patients who have had a coronary thrombosis and healthy controls in respect of some coagulation tests on fasting blood and that taken at the fourth postprandial hour Alternatively, it might be concluded that I have not applied appropriate tests to show up such a difference That postprandial lipæmia is not a precipitating cause of coronary thrombosis is supported by Master et al (1939) who found that the time of onset of symptoms of coronary thrombosis was fairly even throughout the twenty-four hours of the day Had the postprandial effects of fat ingestion played a precipitating part, there must have been some difference of incidence between 3 A M and 7 A M, which period for most people, is that farthest removed from the last meal However, there is a vast difference, discussed more fully elsewhere (O'Brien 1957b), between the clotting-time of stationary blood in a glass tube and the formation of a thrombus in the coronary artery of a live patient It is therefore, perhaps, a little optimistic to attempt to demonstrate a possible difference between patients with coronary thrombosis and healthy controls by such comparatively simple in-vitro tests

Summary

Twenty-one men with coronary thrombosis, aged 10–60, were compared with twenty-one healthy men of similar ages Tests were made before and four hours after a selected fatty meal The tests, including a new test, the heptane-accelerated stypven time, measured the clotting-time by many methods Postprandial changes were found in both groups in all tests, including a highly significant shortening of the clotting-time of whole blood in the presence of powdered glass, whereas the shortening of the clotting-time in glass and in silicone-treated glass was significant only at a 5% level No significant differences between the two groups either before or after the meal were found These findings lend no support to the suggestion that postprandial hypercoagulability is responsible for the alleged connection between the fat-content of the diet and coronary thrombosis

This work was done during the tenure of a grant for technical assistance from the Medical Research Council which I gratefully acknowledge My thanks are due to Mr J A Heady of the Medical Research Council's social medicine unit, for all the extensive statistical analyses and to Mrs J M Cheater A I M L T, *for technical assistance The Russell's-viper venom was kindly supplied* Messrs Burroughs Wellcome & Co

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FLUORESCENT PROTEIN TRACERS

A SIMPLE ALTERNATIVE TO FLUORESCEIN

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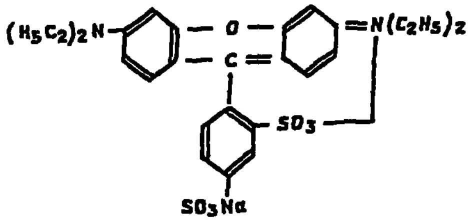
THE Coons technique, using antibody labelled with fluorescein (reviewed by Coons 1956) has been established for some fifteen years Protein conjugates with fluorochromes other than fluorescein have also been tried from time to time—e g, β-anthryl isocyanate (Creech and Jones 1941), 1-dimethylaminonaphthalene-5-sulphonyl chloride and nuclear fast red (Clayton 1954), and rhodamine B isocyanate (Silverstein 1957) None of these materials has been widely used, either because of difficulty in repeating conjugations or because the products compared unfavourably with fluorescein conjugates Nevertheless, fluorescein is not the ideal fluorochrome for tracer work, because the method of conjugation is laborious and the apple-green colour of its fluorescence often contrasts poorly with the blue-green of tissue autofluorescence

We believe that these two disadvantages may be largely overcome by the use of the dye 'Lissamine Rhodamine B 200' (RB 200)



This dye has a brilliant red fluorescence in aqueous solution, in the form of its sulphonyl chloride it can be easily combined with serum-proteins, without denaturing the protein, to yield stable conjugates which have a brilliant orange fluorescence (maximum emission about 610 mμ) in ultraviolet light

Methods

Preparation of Conjugates

1 g of RB 200 and 2 g of phosphorus pentachloride are ground together in a mortar for 5 minutes in a fume cupboard D[illegible] are [illegible] 10 ml is then added and the mixture is allowed to stand fo a

further 5 minutes with occasional stirring, after which it is filtered. The acetone solution of the sulphonyl chloride of RB 200 thus obtained is used promptly because its stability is not at present known, but successful conjugations have been achieved up to 18 hours after preparation.

Conjugation with the protein and subsequent steps are carried out at 0–2°C. Each millilitre of serum, or (for immunological tracing) serum-globulin solution of the same globulin concentration as in the original serum, is diluted and buffered with 1 ml. of physiological saline solution and 1 ml. of carbonate-bicarbonate buffer (0.5 *M*, pH 9.0). Then 0.1 ml. of the acetone solution of RB 200 is added drop by drop, stirring constantly and the stirring is continued for 12–18 hours. The product is dialysed against regular changes of saline solution until dye no longer appears in the dialysate, usually requiring about 6–8 days. The final volume of the conjugate is about three times that of the original serum; if required it may be reconcentrated by exposing the dialysis sac to the draught of a fan.

Conjugated sera are stored at 15° to 20°C and, so far as our observations go, they remain stable under these conditions. When sera are required for immunological tracing they are absorbed with dried liver powder as described by Coons (1956). Activated charcoal is also useful in reducing non-specific staining. Immunological considerations may make absorptions with other materials desirable.

Applications

RB 200 conjugates were used to repeat direct plasma tracing and immunological tracing experiments in which fluorescein conjugates had already been successfully used (Nairn et al. 1957, McEntegart et al. 1957).

For direct plasma tracing, normal serum conjugates, dialysed and reconcentrated to the original volume of serum, were injected intravenously, in the dose 0.8 ml. per 100 g. body-weight, into rats and rabbits, which were killed 2–4 hours later. The animals were either normal or had undergone some procedure known to increase the permeability of membranes—e.g., asphyxia or acute experimental hypertension. Unstained paraffin sections of formalin-fixed tissues were mounted in a non-fluorescent mountant ('Fluormount', Gurr Ltd.) and examined by ultraviolet fluorescence microscopy.

To investigate the suitability of the method for immunological tracing, serum-globulin conjugates were prepared from the following rabbit sera: (1) antibacterial sera (pneumococcus type III, Klebsiella Glaxo 494E), (2) antiprotozoal sera (*Trichomonas vaginalis*, *T. fœtus* var. Belfast and Manley), (3) antiviral sera (cowpox, vaccinia, and fowlpox), and (4) anti-horse serum. This last was used to obtain an accurate measurement of antibody titre before and after conjugation and showed that the titre of the conjugate had been reduced to about half that of the control sample (1/640 to 1/320). The remaining conjugated antisera were applied directly to the corresponding antigens in smears or fresh frozen sections, as in the Coons technique, specific staining being characterised by a brilliant orange fluorescence. The test of specificity was absence of staining in control preparations treated with (*a*) conjugated normal globulin and (*b*) conjugated immune globulin after pre-treatment with an unconjugated sample of the same immune serum. Conjugated anti-rabbit globulin, prepared from goat serum, was also applied successfully to detect rabbit antibody previously fixed to the appropriate antigen.

When double tracer experiments were undertaken using both RB 200 and fluorescein conjugates, the material under test was treated with the RB 200 conjugate for 30 minutes and then rinsed and washed in neutral buffered saline solution for 5 minutes. The specimen was then treated with the fluorescein conjugate for 20 minutes, rinsed and washed for 10 minutes, and mounted in buffered glycerol. The order of application of the conjugates may be reversed, and the times are not critical.

Microscopy

This was done with the Reichert fluorescence microscope using a high-pressure mercury-vapour lamp as the source of ultraviolet light.

The lamp may be screened to emit (*a*) ultraviolet rays of wavelength 280–410 mμ with maximum intensity at 365 mμ, necessitating only an ultraviolet stopping filter above the object, and (*b*) ultraviolet + blue light up to a wavelength of 475 mμ, necessitating the use of a yellow filter above the object to obtain a black background. With the latter system the intensity of the orange fluorescence of the RB 200 conjugate is much increased, and at the same time the yellow filter enhances the contrast with the blue-green of autofluorescence. This is not, however, an advantage in double tracer experiments where fluorescein conjugates are also used, since it reduces the contrast at the green end of the spectrum; here the use of ultraviolet rays alone is better.

Although the above-described methods of preparation, application, and microscopy give satisfactory results, there is scope for further experiment to decide the optimum conditions.

Results

Properties of RB 200 Conjugates

Conjugation of the dye to the protein does not appear to have had any material effect on the biological properties of the protein molecule. No toxic effects were observed in 16 of 17 animals injected intravenously with the tracer dose of conjugated serum. In the remaining animal, a rat which received conjugated rabbit serum, a hypersensitivity reaction took place, but this may have been due to the heterologous protein rather than to the dye. The rate of elimination from the circulation of conjugated homologous albumin has also been studied in 2 rabbits, and the results are similar to those obtained by Schiller et al. (1953) with fluorescein conjugates in rats. Conjugated sera compared with the sera before conjugation (6 experiments) have shown no significant difference in their paper electrophoretic patterns.

Direct Plasma Tracing

The RB 200 conjugate has provided an efficient plasma label which compares favourably with fluorescein conjugates because it contrasts better with tissue autofluorescence and also permits the use of a more intense illuminating system. When it is used as a simple plasma tracer in normal animals, its distribution is the same as that of fluorescein conjugates: histological examination by fluorescence microscopy has shown orange fluorescence in the vascular system and in high concentration in the Kupffer cells of the liver. In pathological states the RB 200 conjugate has provided an excellent marker of damage to membranes: the fluorescent cytoplasmic droplets found in damaged liver-cells in tracer studies with fluorescein conjugates (Nairn et al. 1957) are more readily detected when RB 200 conjugates are used. Double-tracer experiments have also been carried out using conjugates of both RB 200 and fluorescein—e.g., a rat, which developed hypersensitivity œdema after the intravenous injection of whole rabbit serum conjugated with RB 200, was given, 90 minutes later, a fluorescein conjugate; it was killed after a further 30 minutes. Sections of the subcutaneous tissue showed a considerable quantity of RB 200 conjugate in the connective tissue and lymphatics, whereas the fluorescein conjugate was confined to the blood-vessels. In this experiment the technique provides striking visual evidence that capillary leakage of plasma had occurred and that it had been transient.

Immunological Tracing

Conjugated immune globulins tested against the corresponding antigens show a staining specificity similar to that of fluorescein conjugates. Different antigens in the same preparations may be clearly demonstrated by the successive application of RB 200 and fluorescein conjugates of the appropriate antisera. This technique has been successful in a number of experiments including the demonstration of pneumococci and Klebsiella simultaneously in mouse-tissue sections and the identification of individual protozoa in mixed films of the Belfast and Manley strains of *T. fœtus*. The evidence we have so far obtained suggests that, in the staining of virus preparations, RB 200 conjugates behave in the same way as fluorescein conjugates.

Comment

Serum-protein conjugates with RB 200 are as useful as fluorescein conjugates for direct and immunological tracing. They have the advantage that their preparation is simple, requiring no special laboratory facilities, and their colour contrasts well with tissue autofluorescence. RB 200 therefore offers an attractive alternative to fluorescein. Furthermore, the orange fluorescence of RB 200 conjugates is sufficiently different from the apple-green of fluorescein conjugates for them to be used together in double-tracer experiments, they may be applied either as simple plasma labels or as immunological stains.

This research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust. We also wish to thank Imperial Chemical Industries for supplying the 'Lissamine Rhodamine B 200', the department of bacteriology, University of Liverpool, for the pox virus antisera, Dr Muriel Robertson for the cultures of T. fœtus. Finally, we are indebted to Prof W. O. Kermack, Prof A. Macdonald, and Prof J. S. Young for their helpful advice, and to Miss Jane C. Hardie and Mr S. Kinnaird for technical assistance.

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Preliminary Communication

RESPONSE OF THE ADRENAL CORTEX TO CORTICOTROPHIN FROM HUMAN INFANTILE PITUITARY GLANDS

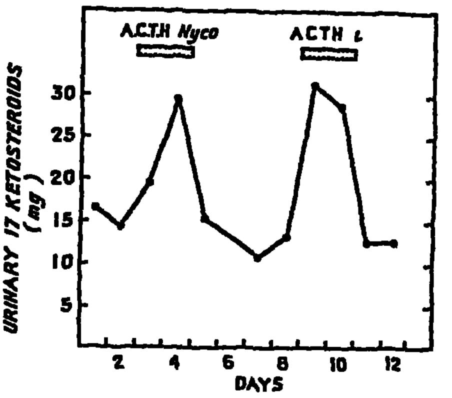
IN man the daily output of 17-ketosteroids in the urine is low during the first 6–8 years of life, after which it increases rapidly to adult levels. In children the ratio of the corticoids to the 17-ketosteroids in the urine differs considerably from that in adults. The underlying cause of the rapid increase in the urinary excretion of 17-ketosteroids just before puberty (the period termed adrenarche) is still obscure.

Talbot et al.[1] presented data indicating that corticotrophin consists of two different trophic factors: one stimulating production of the 11-17-oxysteroids throughout life, and the other stimulating that of the adrenocortical 17-ketosteroids. They suggested that infants and children usually excrete almost no 17-ketosteroids, because their adrenal cortices are not stimulated by corticotrophin capable of stimulating the production of the normal adult type of precursor of 17-ketosteroids.

Ferrazzini et al.,[2] who found that the average percentage increase of urinary excretion of 17-ketosteroids by children treated with corticotrophin was about the same as that of adults, concluded that the capacity to secrete precursors of urinary 17-ketosteroids (the so-called androgenic function) is fully developed in the adrenal cortex of children. They emphasised that their findings supported the suggestion of Talbot et al.

Carletti and de Barbieri[3] conclude that the adrenal cortex of children in the first months of life is functionally mature for the secretion of androgens.

Sprechler and colleagues[4-5] found only a very slight increase of urinary 17-ketosteroids in children treated with corticotrophin: the younger the child the smaller was the increase. They thought that this slight increase was due to relative immaturity of the adrenal cortex, the ability to produce 17-ketosteroids or their "true precursors" being deficient.



Effects of administration of commercial corticotrophin (A.C.T.H. 'Nyco') and of corticotrophin from infants' pituitary glands (A.C.T.H.-I) on urinary excretion of 17-ketosteroids in a man aged 57.

Thus the results of previous investigations are conflicting. Accordingly we decided to prepare corticotrophin from the pituitary glands of infants and then to stimulate adult adrenal glands with this material. If this caused a considerable increase in urinary 17-ketosteroids, there could be no lack of a tropic factor stimulating the production of 17-ketosteroids in the pituitary glands of infants, and there would be no need to postulate two kinds of corticotrophin.

Method

We collected 74 pituitary glands at necropsies on infants, aged less than 2½ years, with no evidence of a primary endocrine disorder. Most of the babies had died at or soon after birth. Their pituitary glands were immediately placed in cold absolute acetone. A powder was subsequently prepared by extraction with acetone and drying over phosphorus pentoxide. The dried powder weighed 1.3241 g. and yielded 128.8 mg. of corticotrophin with an activity of 0.4 I.U. per mg.—i.e., a total activity of 51.5 I.U.

Clinical Test

In January, 1957, an opportunity arose to test this preparation of corticotrophin in a man, aged 57, who had no known endocrine disorder. He had previously been given intramuscular '*Acthar-Gel*' 40 I.U. twice daily for two consecutive days, and his daily urinary excretion of 17-ketosteroids and 17-ketogenic steroids had reached 28 mg. and 82 mg. respectively, estimated by the method of Norymberski modified by Diczfalusy et al.,[6] which was used in all the estimations mentioned here. The effects of the corticotrophin obtained from infants' pituitary glands (A.C.T.H.-I) and of commercial corticotrophin (A.C.T.H. 'Nyco') on the urinary excretion of 17-ketosteroids and 17-ketogenic steroids were compared (see figure).

On days 3 and 4 the patient received 25 I.U. of commercial corticotrophin intravenously in sixteen hours. His urinary excretion of 17-ketogenic steroids increased to 84 mg. and of 17-ketosteroids to 30 mg. in twenty-four hours. The corticotrophin made from pituitary glands of infants, given in the same way as the commercial corticotrophin, increased his urinary excretion of 17-ketogenic steroids to 91 9 mg and of 17-ketosteroids to 32 8 mg in twenty-four hours

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[1] Talbot, N. B., Wood, M., Campbell, A. M., Christo, E., Zygmuntowicz, A. S. in Proceedings of the Second Clinical A.C.T.H. Conference (edited by J. R. Mote); vol. I, p. 40. London, 1951.
[2] Ferrazzini, F., Borth, R., Mach, R. S. *Helv. pædiat. acta*, 1952, 7, 60.
[3] Carletti, B., de Barbieri, A. *Minerva med.* 1953, 5, 1067.
[4] Sprechler, M. Investigations on the Urinary Excretion of Adrenal Cortical S[illegible] p. 139. Copenhagen.
[5] Sprechler, M., [illegible] J. *Acta endocr., Copenhagen*, 1953, 12, 20[illegible]
[6] Diczfalusy, E., Plantin, L. O., Birke, G., Westman, A. *ibid* 1955, 18, 3[illegible]

On the evenings of days 3 and 9, and all through days 4 and 10, no circulating eosinophils were found in his blood

From these observations it is clear that corticotrophin made from the pituitary glands of infants did not lack a " 17-ketosteroid stimulator "

Comment

Since corticotrophin made from pituitary glands of infants considerably increased the urinary excretion of 17-ketosteroids in an adult, it is most probably the capacity of the adrenal glands of infants and children to elaborate 17-ketosteroids that limits production of these hormones in infants and children, but there are two alternatives (1) the pituitary gland of the child does not secrete the 17-ketosteroids stimulator before the adrenarche, and (2) the infantile pituitary gland contains a factor which is not the same as the corticotrophin prepared in this investigation by accepted methods Most probably, however, the underlying cause of the adrenarche in man is to be found in the maturing of the adrenal cortex

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New Inventions

A LOW-RESISTANCE RESPIRATORY VALVE

Measurements of ventilation involving high rates of flow are influenced by the resistance of the measuring apparatus This is certainly true of tests of maximal breathing capacity [1] and probably true of measurements of minute ventilation on effort In modifying existing methods of making these tests we could not find any respiratory valves of sufficiently low resistance After considerable trial and error a valve of suitable characteristics was assembled and is described here

The valve, whose design is shown in fig 1, is constructed of acrylic sheet ¼ in thick and of acrylic tube 1 in in internal diameter The valve components (three inspiratory and three expiratory) are commercially available [2] The dead space between the two valve-plates is divided by a median septum so that the actual volume of dead space is greatly reduced The extent to which expired air contaminates the space on the inspiratory side of the septum was tested by sampling continuously from this space with a CO_2 analyser [3] while breathing took place through the valve at different velocities Comparison of the end expiratory CO_2 value at different sites in this space with the end expiratory CO_2 value at the mouth indicates the degree of contamination of the inspiratory side of the septum with expired gas It was calculated that the effective dead space of the valve varied from 25 to 52 ml according to the force of expiration

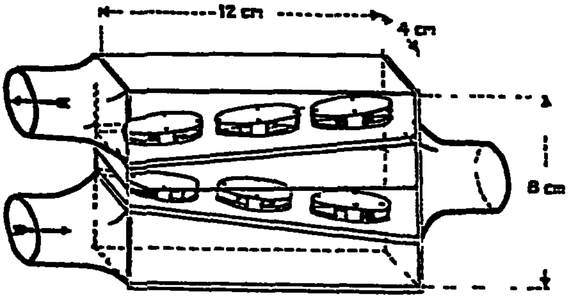

Fig 1—Schematic drawing of the valve

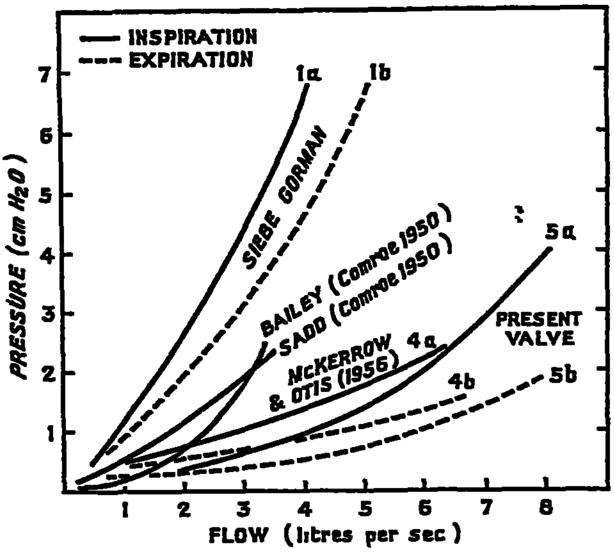

Fig 2—Resistances of various valves

The opening pressure of the valve when wet is 2 mm H_2O and is influenced to a negligible degree by gravity The pressure developed across the valve at different flow-rates compares favourably with other valves tested by us At an inspiratory flow rate of 5 litres a second the pressure developed across double valves of the type developed at the Max Planck Institute was 8 75 cm H_2O, across a Goldman valve 13 0 cm H_2O [4] and across Siebe Gorman valves (cat no EXQUA) 10 8 cm H_2O [5] The equivalent value for the valve described here is 1 6 cm H_2O, as shown by fig 2, where this valve is compared with others whose descriptions have been published [6]

The only valve of comparably low resistance is that described by McKerrow and Otis,[7] which has a much larger dead space (240 ml) Another low-resistance valve was developed by Bannister and Cormack [8] for studying exercise ventilation, but it does not appear suitable for the very high frequencies that may be encountered during tests of maximal breathing capacity, and, since the flaps are gravity-operated, the valve would need somewhat more care in use

This valve is suitable for daily use, it is rugged and can be repeatedly washed with hot water and detergent or disinfectant

Assembled valves of this design may be obtained from J Quick, Medical School, University of the Witwatersrand, Johannesburg, South Africa

This report from the Pneumoconiosis Bureau and from the Pneumoconiosis and Cardiopulmonary Research Units of the C.S I R, Johannesburg, is printed under Government printers copyright authority no 2451 of Aug 12, 1957

J C. Theron
M B Pretoria
S Zwi
M.B W'srand, M R C.P
Maurice McGregor
M D W'srand, M R C.P

Johannesburg
South Africa

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[1] Matheson H W, Spies S N, Gray, J S, Barnum, D R *J clin Invest* 1950 29, 682

[2] Mica spring exhalation valve (R.M.277) obtainable from Safety and Medical Equipment Co Johannesburg South Africa and from Draegerwerk Luebeck Germany

[3] Manufactured by Liston-Becker Instrument Co, Inc., Springdale (Stamford) Conn Model 16

[4] Goldman, H I *S Afr J Lab clin Med* 1955, 1, 126

[5] These values represent the characteristics of one sample of each valve type and are not necessarily representative of the type as a whole

[6] Comroe, J H, Jr Methods in Medical Research, p 79 Chicago, 1950

[7] McKerrow, C. B Otis A B *J appl Physiol* 1956, 8 497

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Reviews of Books

Operative Obstetrics

R Gordon Douglas, professor of obstetrics and gynecology, Cornell University Medical College, William B Stromme, attending obstetrician and gynecologist, Northwestern Hospital and Fairview Hospital, Minneapolis New York Appleton-Century-Crofts 1957 Pp 735 $20

Designed to deal exclusively with the operative phase of obstetrics, this book describes with great care and clarity almost every obstetric manœuvre or operation in ordinary use Photographs and drawings are profuse, and they are arranged not only as illustrations of the text but also as a companion pictorial account of each operation, which may be followed separately There are also chapters on anatomy, preoperative and postoperative care, anæsthesia and analgesia, and the immediate care of the newborn

The operative descriptions and illustrations are, with few exceptions, admirable and helpful The account of the manœuvres for bringing down extended arms in a breech delivery is perhaps not so clear, and Lövset's manœuvre, so often used in this country, is omitted, similarly, descriptions of the methods of dealing with impacted shoulders in a vertex presentation after delivery of the head are less helpful than most sections of the book, and many obstetricians would question the view that "once the head has been delivered, the respiratory tract cleared of mucus and fluid, and the baby permitted a free airway, time becomes an unimportant factor"

The accounts of methods obviously favoured in the United States are interesting and instructive it is surprising, for instance, to learn that the classical cæsarean operation "continues to be performed, largely in elective situations, at the New York Lying-In Hospital in about 20 per cent of cases"

The book is a valuable source of practical instruction for those learning the subject, and an important reference work for practising obstetricians

The Twice-Born

A Study of a Community of High-caste Hindus G Morrison Carstairs, M R.C.P London Hogarth Press 1957 Pp 345 30s

A stay of two years in a Hindu village and long interviews with 37 high-caste adult males have provided Dr Carstairs with a great deal of fascinating information about one section of the Indian population, and this book has been rather fancifully described as a Hindu *Milk Wood* Some readers might find it easier to see the Hindu wood if the trees were not so minutely described in rather heavy English The anthropologist has to choose between using technical language and writing for the non-specialist reader—a course which need not entail loss of clarity or scientific accuracy, since all the technical data can be included in appendices Voltaire apologised aptly for a long letter by saying "I had no time to write a short one" Though Dr Carstairs may have been in the same difficulty, we cannot help feeling that a more attractive and concise exposition of the methods, results, and possible applications of his work would have won him a wider audience, and this type of work should certainly be widely known and discussed For one thing, the psychoanalytical study of human cultures and societies is potentially of great importance in man's efforts to save himself from his own destructiveness

A System of Ophthalmic Illustration

Peter Hansell, M R C.S, F R P.S, F B P A, director of the departments of photography and illustration, Institute of Ophthalmology, London, and Westminster Medical School Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 114 43s

The diagnosis of eye disease depends very largely on the detection of relatively minute signs of disorder the certainty with which such signs may be seen by modern methods of examination, such as ophthalmoscopy, slit-lamp microscopy, and gonioscopy can seldom be made apparent by the ophthalmologist to those outside his specialty unless various techniques of examination are first acquired Teaching, and especially undergraduate teaching, is thereby severely handicapped

The development of illustration techniques is therefore of special importance, and this book by an acknowledged authority is welcome It is addressed primarily to the medical photographer, and a brief chapter on anatomical considerations appears as an introduction to the main matter of equipment for and techniques of photography and cinephotography of the eye The special techniques now possible for keratography, slit-lamp photography, goniophotography, and retinography are given separate attention, and the superiority of the artist in certain directions is indicated

The book is excellently illustrated and provides both an expert guide for the ophthalmic photographer and a reference manual for the medical photographer who only occasionally has to display ocular abnormalities

Operative Surgery

Vol 5 Orthopædic Surgery Editors, Charles Rob, M CHIR, professor of surgery, University of London, Rodney Smith, M S, F R C S, surgeon, St George's Hospital, London London Butterworth 1957 Pp 372 110s

Orthopædic surgery, the subject of this volume, seems to lend itself particularly to tuition by illustration, for the various techniques are presented with greater conviction in this volume than in those already published, which deal with other subjects The illustrations in section 10 (ankle and foot) are an improvement on anything seen so far in this series Orthopædics is not dealt with in its entirety the hand, amputations (apart from those of toes, which are included here), and some aspects of bone-grafting, are to follow

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Blacklock and Southwell A Guide to Human Parasitology for Medical Practitioners (6th ed London H K Lewis 1958 Pp 222 30s) —It is a tribute to practicability and popularity that six editions of this guide have been called for in 27 years Now considerably revised and brought up to date (but not enlarged) by Prof T H Davey, it remains accurate and reliable The difficult question of terminology and the avoidance of those puzzling synonyms which perplex and befog tropical parasitology have been skilfully managed and this alone must make it attractive to the modern student The simple and direct text is a distinct advantage, but it may not always appeal to the advanced student or research-worker The 119 line illustrations and the 3 coloured plates are excellent There is a small point in terminology, which is apt to be confusing, in plate II (fig 17) where a malaria trophozoite is represented within a "punctate basophil", which is surely a misnomer for a stippled erythrocyte New features are brief sections on isospora and *Toxoplasma gondii* There is clearly a demand for this kind of book, which must be regarded as a complement to those textbooks of tropical medicine in which the emphasis is mainly on the clinical aspects

Stedman's Medical Dictionary (19th ed London Baillière, Tindall, & Cox 1957 Pp 1656 88s) —Three years ago Dr N B Taylor and Mr A E Taylor told us "To the creation of medical words there is no end" To the new edition of this familiar dictionary they have added 85 pages covering several thousand new terms, and their publishers say that "about a thousand words a year are added to the medical jargon, and in three years or so you will need a new medical dictionary" We have been warned

Pediatric Profiles (St Louis C V Mosby 1957 Pp 264) —Prof B S Veeder has collected and edited a series of "written pictures" of men who were important in the development of American pædiatrics Most of these men are American, the British names include Sir Thomas Barlow and Sir Leonard Parsons There is also an article on pædiatrics in Vienna early this century

THE LANCET

LONDON 22 FEBRUARY 1958

Long-term Anticoagulant Treatment for Coronary-artery Disease

ANTICOAGULANT treatment for acute myocardial infarction has gained support steadily in the past few years. Last year when HONEY and TRUELOVE[1] attempted to stem the tide, we suggested that their conclusions were unlikely to pass unchallenged and that few physicians would be deflected from using anticoagulants.[2] Subsequent correspondence confirmed this forecast, and it is clear that there is now generally little argument about the value of anticoagulant treatment in the acute episodes of coronary disease. Anticoagulants have significantly increased the number of patients who survive acute infarction, and serious consideration is being given to the prevention of new episodes. How long is the administration of anticoagulants to be continued—for six weeks or for years? Largely because of the development of better anticoagulants and increased experience in the control of anticoagulant therapy, it is definitely practicable to apply long-term anticoagulant therapy in the hope of preventing, or at least postponing, new coronary thromboses in patients who have had one such incident.

Long-term anticoagulant treatment for coronary-artery disease was begun by OWREN in Norway in 1948, and in 1954 he described his technique and his results with 236 patients, half of whom had had one infarction before treatment was begun.[3] In America TULLOCH and IRVING WRIGHT[4] reported results with a smaller group. Both sets of workers were convinced that this form of treatment was worth pursuing. Since then several papers have supported the use of this treatment and pointed out that the risk of bleeding complications is very small and worth taking. KEYES et al.[5] studied 71 patients who had had a single myocardial infarct and 50 who had had recurrent infarcts; these patients had received anticoagulant treatment for up to five years. Their method of comparison with control groups who did not receive anticoagulant treatment is somewhat complex, but they concluded that in the single-infarct group the death-rate was three times greater without anticoagulant treatment than with, and in the recurrent-infarct group the death-rate was five times greater. WAALER[6] in Oslo has lately reported on the results of continuous anticoagulant treatment in 275 patients with angina pectoris who were observed for up to three and a half years (average two and a half years). At first dicoumarol was used, but later phenindione. WAALER concluded that long-term anticoagulant treatment significantly reduced the mortality among his patients, taking for comparison a similarly collected series of patients who had not had anticoagulant treatment at all. The frequency of myocardial infarctions was also clearly reduced. The effort tolerance of the patients was greatly improved in 38%, and slightly improved in a further 12%; this amelioration occurred gradually in the first year of treatment. Hæmorrhagic complications were few; there were only 15 bleeding episodes needing treatment; 3 of these were fatal cerebrovascular accidents, but all 3 patients had hypertension. Of his 275 patients 223 had no bleeding at all.

An interesting account of ten years' experience with long-term anticoagulant treatment has been published by BENJAMIN MANCHESTER.[7] Alternate patients were allotted to the treated or control groups; the treated patients were given dicoumarol or acenocoumarin ('Sintrom'), and otherwise both groups had the same medical care—i.e., diet, digitalis, diuretics, and sedatives when required. Satisfactory records were obtained for 204 patients who had been kept on anticoagulants for one to ten years, and for 200 control patients. The two groups were closely comparable; for example, in the treated group 74% were classified as "poor risks" and 26% as "good risks", while in the control group the figures were 71% and 28%; 25% of the anticoagulant group had had previous myocardial infarction, compared with 20% of the controls. Hæmorrhagic complications were few; of the 204 anticoagulant-treated patients only 6 were affected, and none died of such complications. The incidence of subsequent myocardial infarction was three times greater, and the mortality-rate eight times greater, in the control than in the anticoagulant-treated group. The overall mortality due to thromboembolism and hæmorrhage was 8% in the anticoagulant group and 42% in the control group. On the other hand, the incidence of angina pectoris after infarction seemed to be unaffected by the treatment; the rate was 36% for both groups. More than half of the anticoagulant group showed increased tolerance in walking and with the Masters two-step test; only just over a quarter of the control group improved. MANCHESTER considers that his own and previous reports show that the serious risk of recurrent myocardial infarction after a first attack can be mitigated by anticoagulant treatment. But he is not satisfied with present results, and he rightly points out that, though anticoagulant treatment reduces the incidence of subsequent infarction and of thrombo-embolic complications, the fact that these continue to occur "indicates the limitations of presently available oral anticoagulants."

Results like these inevitably lead to inquiries about extended arrangements for long-term anticoagulant treatment. Such arrangements may not be easy to provide in all general hospitals. TOOHEY[8] has pointed out that "in the control of treatment there are two equally important essentials—adequate laboratory technique and administration of the anticoagulant drug by a clinician experienced in its use."

"Adequate laboratory technique" means reliable estimation of plasma-prothrombin.[9] At present Owren's

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[1] Honey, G. E., Truelove, S. C. *Lancet*, 1957, i, 1155, 1209.
[2] *Ibid*, p. 1339.
[3] Owren, P. *Schweiz. med. Wschr.* 1954, 84, 822.
[4] Tulloch, J., Wright, I. S. *Circulation*, 1954, 9, 823.
[5] Keyes, J. W., Drake, E. H., Smith, F. J. *Ibid*, 1956, 14, 254.
[6] Waaler, B. *Acta med. scand.* 1957, 157, 289.
[7] Manchester, B. *Ann. intern. Med.* 1957, 47, 1202.
[8] Toohey, M. *Brit. med. J.* Feb. 1, 1958, p. 252.
[9] See *Lancet*, 1957, ii, 679.

"P & P" (prothrombin & proconvertin) technique is having some vogue, and its principles and technique have been set out afresh by ALLINGTON[10] The method uses diluted plasma, excess fibrinogen and factor V (proaccelerin) are added in the form of bovine plasma from which factor VII (proconvertin) and prothrombin have been absorbed, the source of thromboplastin is a standardised saline extract of human brain, and buffer solutions are used to keep ionic strengths constant It is claimed for this method that it shows less day-to-day variation than Quick's, and reflects changes in the prothrombin level sooner ALLINGTON thinks that the "P & P" method is valuable for control of all types of anticoagulant therapy, and points out that with it reliable results on specimens sent through the post can be obtained TOOHEY[11] agrees that this test is very useful for the smooth control of the acute and immediately subsequent phases of a myocardial infarction, but for the control of long-term anticoagulant treatment "it is difficult to see how Owren's technique will materially improve on Quick's method Indeed, in a busy outpatient clinic, where large numbers of tests have to be made quickly to avoid keeping the patients waiting too long, the speed and simplicity of Quick's method are a decided advantage" MANCHESTER[7] has a technique of his own devising in which the estimation is made on capillary blood collected from a skin puncture in a hæmoglobin pipette, such a method, obviating venepuncture, deserves careful study

Experience in the use of anticoagulant drugs—TOOHEY's second essential—means that the physician concerned should be regularly treating patients From the large number of drugs available, he may have selected a few and become familiar with their properties, TOOHEY,[8] for example, uses phenindione or warfarin sodium for initial short-term treatment, and dicoumarol or the newer phenylpropylhydroxycoumarin ('Marcoumar') for long-term anticoagulant treatment It should not be difficult in a general hospital to arrange that one physician is responsible for most of the patients needing anticoagulant treatment, and his advice would be available for his colleagues What the patient is likely to find irksome is having blood samples for prothrombin estimation taken at fairly short intervals MANCHESTER had tests done on his patients at least once a month, WAALER[6] considered that the estimations should be done at intervals not longer than three weeks, and OLWIN and KOPPEL[12] at intervals no longer than two weeks Such a programme, extending over years, with fresh cases being added all the time, will surely call for resources that few laboratories at present possess In the American series most of the patients were paying for their treatment, and some physicians have organised home collection of blood specimens for prothrombin estimation, in this country a postal service may prove helpful No doubt, once convinced of the value of long-term anticoagulant treatment, health service authorities will eventually provide the necessary clinical and laboratory facilities No half-measures will be effective

Chemoprophylaxis of Tuberculosis

IN this country, and in others where the incidence and importance of tuberculosis are declining, it is not always realised that of all the infectious and parasitic diseases throughout the world tuberculosis remains in the lead[1] Ten years ago it seemed that widespread B C G vaccination offered the best prospect of controlling it, for vast improvements in living conditions and nutrition could not be expected overnight, and the discovery and segregation of infectious patients by full chest-clinic and hospital services were economically impossible Since then the treatment of tuberculosis has been radically improved, and now it is possible to conceive effective measures to reduce the disease even in the face of poor living standards and little money According to W H O[2] "In vast areas of the world the control of tuberculosis may well eventually depend on the widespread use of cheap drugs for therapeutic and prophylactic purposes"[2] With a communicable disease all effective therapeutic measures are preventive The term chemoprophylaxis is sometimes used rather loosely For instance, last year a W H O study group[3] included under prophylaxis the administration of isoniazid to persons with no evidence of tuberculosis except a positive tuberculin skin reaction This implies that a person infected with tubercle bacilli is not diseased if no lesions have been discovered by our still crude methods of investigation, which is surely an unnecessary extension of the usual meaning of prophylaxis, when such a procedure can just as well be called treatment Indeed, the problem might be seen more clearly if these people were considered diseased[4], for "diseased" implies failure of prophylaxis, and as long as there are people requiring "chemoprophylaxis" there is need for more prevention Antibacterial drugs can make infectious people non-infectious or prevent the non-infectious from becoming infectious, and they may also stop the non-infected from becoming infected, but this is not the sense in which the term is being used in tuberculosis

MITCHISON[5] has analysed some of the factors relevant to the prophylactic use of isoniazid There is, in fact, little experimental evidence It seems likely from observations on animals that isoniazid administered at the time of exposure to tubercle bacilli could completely prevent disease and be a *true prophylactic* In practice, however, this use of antibacterial drugs would be limited to small selected groups—for example, those accidentally infected in laboratories, uninfected nurses exposed to infectious patients for short periods, or uninfected contacts who for some reason were not being vaccinated with B C G CANETTI[6] suggested that isoniazid could be used for immediate protection while immunity was developing from vaccination with an isoniazid-resistant variant of B C G, but there seems as yet no experimental support for this In people with tuberculin skin sensitivity the bacilli may be actively dividing or physiologically inert. If actively dividing they would be susceptible to the bactericidal activity of isoniazid, though if present in large numbers they might not be completely eradicated. ROBINSON et al[7] administered isoniazid to 6 infants with tuberculin skin sensitivity and normal chest radiographs, and observed a change to insensitivity in 4 of them, but this change did not take place in 7 infants who had radiographic abnormalities. If the bacilli are mainly dormant, isoniazid administration would kill them only slowly, and, unless given for very long periods, might not reduce the incidence of spreading disease. MITCHISON points out that the experimental work concerning the effect of isoniazid administration on the development of immunity—which has given discrepant results—is highly artificial and probably irrelevant to the problem in man. The risk of the emergence of resistant strains of bacilli from isoniazid chemoprophylaxis has been much discussed, but again there are few facts. MITCHISON concludes that the risk in the previously uninfected—true prophylaxis—is probably very small, but in the previously infected it might be larger, because of the bigger bacterial populations exposed to the drug, and in those with radiographically manifest lesions it would be larger still.

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[10] Allington, M. J. *J. clin. Path.* 1958, 11, 62

[11] Toohey, M. *Ibid*, p. 56

[12] Olwin, J. H., Koppel, J. L. *Arch. intern. Med.* 1957, 100, 842.

[1] *Epidem. vit. Statist. Rep.* 1957, 10, 351

[2] *Chron. World Hlth Org.* 1957, 11, 305

[3] Chemotherapy and Chemoprophylaxis in Tuberculosis Control. *Wld Hlth Org. tech. Rep. Ser.* 1957, no. 141

[4] See *Lancet*, Feb. 8, 1958, p. 302

[5] Mitchison, D. A. Advances in Tuberculosis Research; vol. 8, p. 231 Oxford 1957

[6] Canetti, G. *Amer. Rev. Tuberc.* 1956, 74, 219

The prophylactic effect of isoniazid in infected childdren has been studied by the U S Public Health Service[8] 1376 children received isoniazid and 1335 had identical inert tablets. About 40% in each group had no evidence of infection other than tuberculin skin sensitivity, and none of the children had any symptoms. Treatment had been continued in some of them for up to thirty months when the report was prepared. Serious extrapulmonary tuberculous complications developed in 5 children receiving isoniazid and in 28 receiving the inert tablets. The risk of these complications increased with the extent of radiographic involvement, it was 6 per 1000 in those without X-ray abnormality and 59 per 1000 in those with manifest lung lesions. In a second trial household contacts in fourteen cities in the U S A are receiving daily doses of isoniazid or an inert tablet, and the subsequent incidence of tuberculosis is being observed.[9] Chemoprophylaxis is being extensively used by ZORINI in Rome.[10]

The W H O study group strongly recommended that more field and laboratory research be undertaken. They suggested that in areas of high tuberculosis prevalence isoniazid be administered to people with tuberculin skin sensitivity who are in contact with infectious cases. They also draw attention to the urgent need to investigate the extent to which uneducated and entirely symptom-free persons will continue taking drugs. It would be worth investigating also the capacity of the educated patient for regular self-medication. A primitive superstitious people may possibly be persuaded to take medicine regularly with greater ease than a sophisticated one. In one report from this country half the outpatients at a clinic were thought on the basis of urine tests to be taking their P.A.S. irregularly.[11] In this report it seemed to be assumed that the patients would take isoniazid more regularly than P A S, but there is no evidence of this. Is not at least some of the defaulting caused by forgetfulness? In all lands responsibility for medication, both for prevention and for treatment, now often rests largely with the patient, and it is important to establish the extent to which patients fail in this, and how much it matters if they do sometimes fail.

Annotations

BIGGER CONTRIBUTIONS

FROM next July the weekly contribution to the National Health Service will be raised by *6d* for men, *4d* for women, and *2d* for juveniles, and their employers will pay an extra *2d*. These increases, the Chancellor of the Exchequer said on Tuesday, will bring in about £24 million in the next financial year, and about £32 million in a full year. From July the total National Health Service contributions for men, women, and juveniles will be *2s 4d*, *1s 8d*, and *1s 4d*, and these contributions, by worker and employer, will pay for just under a fifth of the gross cost of the service, compared with about a ninth at the present time. When the scheme started (Mr Heathcoat Amory said) the intention was that these direct contributions should cover a fifth of all Health Service expenditure, and certainly there are advantages in the public paying from their wages and salaries a significant proportion of what the service costs—especially if they understand what that proportion really is. On the other hand, a fifth of the cost of the service in 1958 is much greater than a fifth ten years ago, and for some families the proposed subtraction of ten shillings from the breadwinner's pay-packet (for National Insurance and National Health) will be about as much as they can stand. The objection to flat-rate compulsory contributions as a means of financing national schemes is that they bear most hardly on those who have least money, and the Government's new requirements will be criticised for their further retrogressive effect. If more money is to be raised in contributions rather than by additional ordinary taxation the time may soon come when it will be impossible to maintain the flat rate, and contributions will have to be related to income.

CULTURAL FACTORS AND MENTAL HEALTH

THE evaluation of "normal" behaviour is one of the great problems facing the psychiatrist for an act or opinion which seems normal to one observer may seem eccentric to another, or schizophrenic to a third. Much has, of course, been learnt from the study of differing cultures and of the required standards therein for example by their survey of the behaviour of some 200 different peoples—a book too little known by those who write on sexual offences and the law—Ford and Beach[12] have added to our understanding of sexual activities. By comparing the incidence and character of mental disease in races with different customs, and indeed in subgroups of the same people, the cultural approach may reveal ætiological factors in mental disease The study of mental illness in underdeveloped countries may help their governments to plan psychiatric services and to train staff to the best possible effects Such studies might, also, assist in inter-racial understanding and ultimately have implications for international politics

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[7] Robinson, A., Meyer, M., Middlebrook, G. *New Engl. J. Med.* 1955, 252, 983.

[8] United States Public Health Service. *Amer. Rev. Tuber.* 1957, 76, 942.

[9] Palmer, C. E. *Bull. int. Un. Tuberc.* 1957, 27, 364.

[10] Zorini, O. *ibid.* 1957, 27, 330.

[11] Dixon, W. M., Stradling, P., Wootton, I. D. P. *Lancet*, 1957, ii, 871.

[12] Ford, C. S., Beach, F. A. Patterns of Sexual Behaviour. New York, 1951; London 1952.

Some of these topics were discussed at the Royal Society of Medicine on Feb 11 by the Section of Psychiatry, to which Dr G M Carstairs presented some conclusions from a year's psychiatric and anthropological study of a village community in India The idea that some peoples are immune from psychosis, he said, has now died careful study has always shown that mental illness exists even though it may not be recognised as such by the community In the most careful study of a relatively primitive community yet made, Lin[13] found in Formosa an incidence of mental disease remarkably similar to that in Scandinavia and elsewhere, though psychotic depression was somewhat less prevalent This infrequency of depression, noted as long ago as 1904 by Kraepelin on a visit to Java, was observed also by Dr Carstairs in Indians, though he suggested that a true endogenous depression may appear in disguised form—e g, in the phenomenon of *amok* in Malays, which passes from a phase of sulking and withdrawal to a deliberate suicide in which the victim takes as many with him as he can Though schizophrenia has been found to take different forms with delusional content appropriate to the cultural background, the atmosphere in the Indian mental hospital is remarkably like that of the European, with mania, catatonia, and depressive stupor clearly seen—a point underlined by Prof W Mayer-Gross in the discussion With the neuroses, however, no such familiar pattern is evident, and it appears that cultural factors strongly affect the form of illness hysterical dissociation states of gross degree were common, and there was a condition called *jiryan*, characterised by exhaustion, impotence, inertia, and complaints of wasting, which occurs frequently, resists treatment, and is ascribed by the patients to a leaking away of seminal fluid In India, fear plays a great part in illnesses—whether fear of witchcraft, devils, or sudden death Treatment must take this into account, and it must also allow for the advice on daily routine which the patient expects

Dr Carstairs finally brought the topic nearer home by speaking of the difficulties of the overseas student in this country, separated from his large family for the first time in his young life, studying in a foreign language and amid an alien culture a subject which does not always interest him A mild paranoid reaction is common, and kindly understanding is essential in handling problems as they arise Even nearer home, within our Anglo-American society, there are cross-cultural problems, as illustrated by Hollingshead and Redlich's[14] demonstration that different use of language and a different sense of values may hinder the middle-class therapist's treatment of the working-class patient Though sociological investigations are proceeding, we lack precise knowledge of customs and beliefs in some parts of our own culture While the mental mechanisms discovered by Freud and others may perhaps be universal, life experience varies greatly, and the relevance of this to subsequent symptomatology is not clearly known It must be recognised that the bulk of psychoanalytic knowledge still related largely to a limited stratum of a very small number of societies

Until further work is done, the practising psychiatrist here and in foreign parts can do little more, as Dr Carstairs said, than do his best to see the situation in some measure, from the patient's point of view

SPINAL ANÆSTHESIA

Mr Lake's plea this week (p 387) for renewed interest in spinal anæsthesia once more draws attention to a controversial subject The virtues of this method, which requires only a single, simple injection, comprise localised anæsthesia, relaxation, absence of venous congestion, and contraction of the intestines—qualities of special value during intra-abdominal operations As a whole they cannot be gained to the same extent with any form of general anæsthesia, and certainly not without administration of several drugs They are, however, together rarely essential for the success of any operation, and can be achieved by spinal anæsthesia only at the risk of complications

The commonest sequels are headache and backache 10 to 15% of all patients submitted to this form of anæsthesia have headache subsequently, and some of these have ocular or auditory difficulties Backache is far from uncommon None of these complications is likely to be permanent, but they may last for several months, and often cause considerable hardship even when their duration is short[1] They can be likened to the postanæsthetic sickness and sore throat that equally commonly follow general anæsthesia, but neither of these is so persistent The rarest and most devastating complication of spinal anæsthesia is permanent paraplegia or more localised paralysis, there may be other minor, though usually temporary, neurological sequels[2]

Mr Lake rates the notoriety given to the permanent neurological complications of spinal anæsthesia as the principal reason for its decline in popularity in Great Britain, with, close behind, the introduction of muscle-relaxant, hypotensive, and other drugs It is also true that the longer duration of many present-day operations, and the more leisurely pace of some surgeons, cannot be covered by a single subarachnoid injection of local anæsthetic, and continuous injection through an indwelling needle or catheter is likely to increase the incidence of neurological troubles Moreover, few patients relish the idea of a major operation while awake, and many surgeons are unwilling or unsuited to operate on a conscious patient Light general anæsthesia can usually be safely combined with spinal, but its use in this way detracts from the overall advantages of purely regional anæsthesia

Although all these factors have undoubtedly contributed to the decreased use of spinal anæsthesia, the general availability nowadays of trained anæsthetists is probably of greater importance, for they are able to satisfy the needs of most patients and surgeons by general methods The incidence of most complications of spinal (as of general) anæsthesia can be reduced by care and attention to detail and with experience of the technique, and it might be supposed that in competent hands there would be little to choose between the two on the score of morbidity This is not so There is ample evidence that the temporary and permanent complications of general anæsthesia can be reduced without undue difficulty,[3] but the problem of eliminating the risk of paraplegia after spinal anæsthesia is, as Lake admits, unsolved, and it must be accepted that, even when errors of technique are excluded, subarachnoid injection of a local-anæsthetic drug may lead to permanent damage We remain convinced [4] that this hazard, however rare, should be accepted only in cases where other methods of anæsthesia are unsuitable

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[13] Lin T *Psychiatry* 1953 16 p 313
[14] Hollingshead A B, Redlich F C in the press

[1] Vandam L D, Dripps R D *J Amer med Ass* 1956 161
[2] Vandam L D, Dripps R D *Surgery* 1955 38, 463

BEHÇET'S DISEASE AND THE NERVOUS SYSTEM

In a series of papers published between 1937 and 1940 Behçet [5–8] described the classical features of the disease which is now named after him This has three main features ulcers in and around the mouth, ulcers on the genitalia, and involvement of the eyes The lesions occur in acute attacks, lasting from one to four weeks, and usually recurring several times a year, there is little constitutional disturbance In the mouth painful superficial ulcers covered by a greyish-yellow slough appear on the lips, gums, tongue, palate, or buccal mucosa In the genitalia the scrotum or labia are most commonly involved, but ulcers may also develop on the penis or in the vagina and in the perineum The lesions usually start as small papules or vesicles which rapidly ulcerate, and when they heal there may be scarring, these ulcers are often accompanied by enlargement of the inguinal glands but not by urethritis The commonest ocular lesion is iritis, which may involve one eye before the other, but choroiditis and vitreous and retinal hæmorrhages are not uncommon, and in many cases as a result of recurrent attacks the visual acuity progressively deteriorates and eventually the patient may become blind Rarer features of the disease are erythema nodosum, which affects about a third of the patients, furunculosis, thrombophlebitis, usually in the legs, and pain in the joints, sometimes accompanied by an effusion It has been suggested [9] that this disorder was described by Hippocrates In the third book of *The Epidemics* [10 11] he refers to a disease in which there were aphthous ulceration in the mouth, " defluxions " about the genital parts, ulceration and boils in the groins, and chronic painful inflammation in the eyes The main difference from what is now called Behçet's disease is the description of fungous growths on the eyelids which might lead to blindness and also growths on the genital ulcers

Involvement of the nervous system in Behçet's disease was first described by Knapp in 1941,[12] and since then fourteen or fifteen cases have been reported, including two from Wales by Pallis and Fudge [13] and three from the London Hospital by Wadia and Williams [14] Neurological involvement appears to develop after other lesions have been present intermittently for two or more years, and as with the mucocutaneous and ocular lesions acute episodes with remissions are usual The neurological picture is varied, but so far no instance of peripheral neuropathy or cerebellar involvement has been reported In some patients there has been an acute onset of meningo-encephalitis with fever, headache, meningeal irritation, and signs of central nervous (usually brain-stem) involvement, in these patients there has been an increase of cells in the cerebrospinal fluid, lymphocytes nearly always predominating In other patients neurological involvement may develop more slowly, often with remissions and relapses, causing progressive disability In these, too, the brain-stem is usually affected, but there may also be parkinsonian signs and progressive dementia with epilepsy In these more chronic cases the cerebrospinal fluid is either normal or contains a slightly increased number of lymphocytes The diagnosis may be difficult, the more acute cases resembling tuberculous meningitis or a virus encephalomyelitis, and the more chronic ones disseminated sclerosis Possibly these cases are commoner than the relatively few published reports would suggest, for if the mucocutaneous lesions have healed or are slight, the possibility of Behçet's disease could easily be overlooked The disorder may cause considerable disability from the recurrent oral and genital ulcers and failure of vision from the ocular involvement, and several patients with neurological involvement have died McMenemey and Lawrence [15] have described the pathological findings in two patients There were multiple small lesions, with a predilection for the hypothalamus and brain-stem, consisting of small softenings related to the smaller blood-vessels and rather commoner in the white matter than in the grey There was also some perivascular infiltration with lymphocytes and microglial cells, but changes in nerve-cells were slight, no intranuclear inclusion bodies were found, and there were no definite capillary or venous thromboses

There have been various conjectures about ætiology such as that it is a primarily vascular disorder, an allergic reaction, or a virus infection Behçet claimed to have found inclusion bodies in smears of hypopyon fluid and in the exudate from ulcers in the mouth which suggested a virus infection, but Jensen [16] was unable to confirm these findings Sezer [17] in 1953 claimed to have isolated the virus from the vitreous of an enucleated eye and from subretinal serous fluid obtained by puncture from the other cases, and to have transmitted the virus to laboratory animals, causing encephalitis in mice by intracerebral injection and chorioretinitis in rabbits by injection into the vitreous fluid He also claimed that the material gave strongly positive complement-fixation and neutralisation reactions with the sera of twelve patients suffering from Behçet's disease but not with the sera of healthy controls Later [18] he isolated a virus from the blood and urine of twenty patients with the disease in an active phase There was no confirmation of a virus origin till 1957, when Evans et al [19] obtained a virus from a mixture of cerebrospinal fluid and brain-tissue and from aqueous fluid obtained at necropsy they were unsuccessful with blood, urine, cerebrospinal fluid and fluid from the anterior chamber of the eye, obtained from another patient during life They were able to culture the virus but not to transmit it to laboratory animals They found that the sera of six out of eleven patients with Behçet's disease had virus-neutralising antibody to a titre of 1/32 or more, while the sera of fourteen healthy controls had no detectable neutralising antibody These findings, if confirmed in further cases, will be strong evidence that this peculiar disorder is caused by an infection

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[3] Edwards, G, Morton, H J V, Pask, E A, Wylie, W D *Anæsthesia*, 1956 11, 194

[4] See *Lancet*, 1951 i 516

[5] Behçet H *Derm. Wschr* 1937 105, 1152

[6] Behçet, H *Bull Soc franç Derm Syph* 1938, 45 420

[7] Behçet H *Ibid* 1939 46, 674

[8] Behçet H *Derm.* [illegible] 1940 81 73

[9] Feigenbaum, *Brit J Ophthal* 1956 40 355

[10] Adams, F Genuine Works of Hippocrates vol 1, p 403 London 1849

[11] Jones W H S Hippocrates with an English translation vol 1 p 245 London 1923

[12] Knapp P *Schweiz med Wschr* 1941 71 1288

[13] Pallis C A, Fudge B J *Arch Neurol Psychiat* 1956 75, 1

[14] Wadia N, Williams, E *Brain*, 1957 80 59

[15] McMenemey W H, Lawrence, B J *Lancet* 1957 ii, 353

[16] Jensen, T *Acta derm.-venereol Stockh.* 1941 22, 64

[17] Sezer F N *Amer J Ophthal* 1953 36, 401

[18] Sezer, F N *Ibid* 1956, 41, 41

[19] Evans A D, Pallis C A, Spillane, J D *Lancet*, 1957 ii 35

THE NAME'S NOT THE SAME

BACTERIAL nomenclature is not static, for it is influenced by trends in classification One function of *Bergey's Manual* is to serve as a guide to the naming of bacteria, and its usage is followed closely by almost all American bacteriologists, increasingly by bacteriologists in Europe, and by biochemists in this country In this country the National Collection of Type Cultures has published lists of the species it maintains, and these lists have, like *Bergey's Manual*, served as guides The publication of a new edition of the *Manual*[1] and of a *Catalogue of Species*[2] in the National Collection of Type Cultures has almost coincided

Inevitably there are differences in the names used for some of the bacteria, but, since the compilers of both publications claim to be inspired by the Bacteriological Code of Nomenclature and by the opinions expressed by the appropriate international committee, they are surprisingly numerous even among the commoner bacteria of medical interest Some differences in naming are due to differences in classification, for example, in the N C T C Catalogue the glanders bacillus and Whitmore's bacillus are both in the same genus, *Loefflerella*, but in the *Manual* the first appears as *Actinobacillus mallei* and the second as *Pseudomonas pseudomallei* *Chromobacterium violaceum* of the N C T C, based on the work of Sneath,[3] grows at 37°C and corresponds with *C janthinum* of the *Manual* Bergey's *Chromobacterium violaceum* is Sneath's *C lividum*, and will not grow at 37°C The classification (and naming) of the paracolon bacilli is treated differently in the two works, the *Manual* has one genus, *Paracolobactrum*, for all paracolons, but the N C T C follows the recommendations of the Enterobacteriaceæ subcommittee, and recognises several groups and introduces names such as *Arizona arizonæ* and *Hafnia alvei* The differences are as follows

Bergey	*N C T C Catalogue*
Actinobacillus equuli	*Achromobacter equuli*
Pseudomonas pseudomallei	*Loefflerella pseudomallei*
Aeromonas hydrophila	*Pseudomonas hydrophila*
Escherichia freundii	*Citrobacter freundii*
Aerobacter cloacæ	*Cloaca cloacæ*
Paracolobactrum aerogenoides	*Hafnia alvei*
Paracolobactrum arizonæ	*Arizona arizonæ*
Serratia marcescens	*Chromobacterium prodigiosum*
Shigella schmitzii	*Shigella dysenteriæ* type 2
Shigella arabinotarda	*Shigella dysenteriæ* types 3–6
Shigella alkalescens	*Escherichia alkalescens*
Shigella dispar	*Escherichia dispar*
Pasteurella multocida	*Pasteurella septica*
Hæmophilus hæmoglobinophilus	*Hæmophilus canis*
Actinobacillus mallei	*Loefflerella mallei*
Sphaerophorus necrophorus	*Bacteroides necrophorus*
Diplococcus pneumoniæ	*Streptococcus pneumoniæ*
Corynebacterium pseudodiphtheriæ	*Corynebacterium hofmannii*
Erysipelothrix insidiosa	*Erysipelothrix rhusiopathiæ* *Erysipelothrix muriseptica*
Chromobacterium violaceum	*Chromobacterium lividum*
Chromobacterium janthinum	*Chromobacterium violaceum*

Both lists agree in the naming of most organisms, and it is a pleasure to record that *Micrococcus pyogenes* var *aureus* of the *Manual*, and *Staphylococcus pyogenes* of the N C T C *Catalogue* have both disappeared and are replaced by *Staphylococcus aureus* The "*B coli*" of our youth is now *Escherichia coli*, and Shiga's dysentery bacillus is *Shigella dysenteriæ* serotype 1

Most virus workers will welcome the deletion of viruses from the *Manual*, this will probably make easier the transition from the vernacular to a more scientific nomenclature for these "microorganisms"

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[1] Bergey's Manual of Determinative Bacteriology 7th ed Edited by R S BREED E G D MURRAY and N R SMITH London Baillière Tindall & Cox 1957 Pp 1094 £6

[2] The National Collection of Type Cultures Catalogue of Species M R C memorandum no 35 H M Stationery Office Pp 33 2s 6d

[3] Sneath P H A J gen Microbiol 1956 15 70 Int Bull bact Nomen Taxon 1956 6 65

CONTROL OF DANGEROUS DRUGS IN HOSPITAL

THE Central Health Services Council, impressed by the hazards of careless handling in hospitals of dangerous drugs and poisons, set up a subcommittee to consider the control of these substances Foremost among the subcommittee's recommendations[1] is one that no hospitals should be entirely without the services of a pharmacist, and that the purchase and storage of dangerous drugs and the inspection of ward drug cupboards should always be under the control of a pharmacist The subcommittee emphasises that drugs should not be administered without a written prescription The relevant Acts make it quite clear that only in real emergency can they be administered on verbal or telephoned instructions, and that the order must be confirmed by a written prescription within twenty-four hours This provision is too often neglected, and not uncommonly nurses administer drugs on their own initiative

The subcommittee recommends that the abbreviations P R N and S O S, being open to more than one interpretation, should be abandoned, that a uniform ward order book should be used throughout the National Health Service, and that the dose of medicine administered should be checked against the original prescription, and, when a new prescription sheet is started, all the drugs which the patient is receiving should be brought forward on to it It often happens that administration of a medicine once prescribed is continued until the prescription is cancelled by the doctor

The subcommittee reasonably suggests that medicines other than poisons, and also reagents, disinfectants, and so forth, be kept in locked cupboards Its condemnation of the practice of some sisters of accumulating unofficial stocks is justified Most hospital pharmacists will have seen, during ward inspections, drugs which are out of date and potentially dangerous, such stocks are often stored in improperly labelled containers, and prohibition of relabelling of drugs by nurses is an essential precaution

The subcommittee has done a valuable service in devising a reasonable code for the control of dangerous drugs and poisons in hospitals General adoption of its recommendations would greatly reduce the risk of accidents or misuse

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[1] Central Health Services Council Report of the Joint Sub-committee on the Control of Dangerous Drugs and Poisons in Hospitals H M Stationery Office Pp 25 2s

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THE INDEX and title-page to Vol II, 1957, which was completed with THE LANCET of Dec 28, is to be issued next week A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of THE LANCET, 7, Adam Street, Adelphi, W C 2 Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now

Special Articles

SHADOW AND SUBSTANCE

Some Changes in the Mental Hospital

J A R BICKFORD
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IF one cannot visit a mental hospital and does not know any member of the staff, it is hard to say whether it is good or not One can make some sort of guess from the published work which comes from it, but this is not a very reliable means of judging its merit from the standpoint of the worried parent or the patient who is seriously ill Many hospitals try to provide full information about their activities, and their reports at least give an idea of what they regard as evidence of creditable activity

Some years ago great stress was laid on the number of pathological investigations made within the hospital, later on, particular attention was drawn to the physical methods of treatment available Then the emphasis shifted to increase in the number of admissions each year and the number of outpatient clinics held Today every hospital that wants to be thought progressive announces that most of its wards are open and that a high proportion of its population are voluntary patients But these two last criteria are, like the others, fallible, and there is some risk that they may mislead both the public and the medical profession

APPEARANCES DECEPTIVE

If one takes the trouble, almost every long-stay patient can be persuaded to sign a voluntary-patient form Some will do this because they think that they will then be masters of their fate, but most will sign it because they would sign any piece of paper put in front of them if spoken to firmly enough From the psychiatrist's point of view there are big advantages in having as many patients as possible voluntary For one thing, he is freed from the burden of having to examine them for the statutory renewal But, though this saves the psychiatrist trouble, it is of disservice to the patient because it deprives him of one more safeguard If a renewal has to be written, the patient must be examined, and occasionally he will have some fresh method of treatment recommended or may even be found fit for discharge Sometimes the Board of Control will decide that the grounds for further detention are insufficient and will order his release

Many so-called voluntary patients are in fact chronic schizophrenics who have little idea of where they are or what they are doing, and have no more understanding of their new status than of their old Moreover, a voluntary patient who wants to leave hospital but is not fit to exercise his rights will be told quite frankly that he cannot go If he tries to leave the ward, a nurse will bar the way and he will find himself in bed with his clothes hidden away until he desists from any attempt to use his privileges to leave when he wants to—a privilege, which he very likely did not seek and which was thrust on him for the good name of the hospital

Like voluntary status, the open ward is by no means always what it seems One sees, for example, the open ward containing fifty voluntary patients who never leave it except on their visit to hospital entertainments, and then well-escorted, or the open ward where ten or more of the patients are always to be found in bed because otherwise they would run away There are open wards whose patients are by day turned out into an airing-court with a high iron railing with locked doors in it If the patients want to reach the grounds on the other side of the rails they have to go up an iron staircase from the court to their own ward, and then down a staircase from it to reach another ward From this a passage leads to the main entrance, where a porter may be standing No great difficulty for an R A F prisoner-of-war perhaps, but not what one thinks of when one reads of open wards

Admittedly, to be confined to an unlocked ward is less repressive than to be confined to a locked one, but nobody should imagine that a patient is necessarily free just because his ward door is not locked

A SUBSTITUTE FOR TREATMENT?

But the fact that it is sometimes deceptive is not the most important objection to the policy of opening doors and calling patients voluntary It has other and more serious implications

As children, we used to read of how desperate criminals in the Far East could be kept in paper cages and be trusted not to escape, and in a way the same sort of thing is happening in some of our unlocked wards In general, patients in mental hospitals are not restless and anxious to leave, on the contrary, they are prepared to stay wherever they may happen to be Most of the running away is done by a few, and experience in many hospitals shows that if the wards are unlocked the main incentive to leave has gone, even if the patients are not allowed out of the ward unless escorted

The danger that arises when open doors and voluntary status become the order of the day is that they may be accepted as an alternative to actually treating the patients —an alternative to any serious attempt to make them fit to go home If he is not treated, a schizophrenic patient whose illness is of long standing can deteriorate in an open ward as much as in a closed one, and to call him a voluntary patient is just as useful as calling him the Emperor of the Indies It seems to me that there is still a steady current of opinion against *treating* long-stay patients, and the policy of the open door makes it, if anything, easier to avoid necessary action

Of the difficulties facing the psychiatrist who is anxious to care well for his patients, none are so great as those within himself Indeed, his greatest failing may arise from his greatest virtue He may work very hard and with skill and enthusiasm create (there can be no other word for it) from the raw materials of his hospital a therapeutic community But, because he has made something good, he may become unwilling to change it radically He may fail to see that the instrument he has created is not perfect for all time—that as the culture of the hospital changes so must the therapeutic weapons alter A hospital may be ahead of all others in the 1920s, level in the 1940s, and far behind in the 1960s

Yet there is always room for attempting improvement In the hope of finding a daily routine which for a time at least is more helpful to the patients, small changes and ventures are not to be despised, and it may perhaps be useful to describe one or two developments with which we have lately experimented

SMALL THERAPEUTIC CHANGES

In our hospital of a thousand beds none of the wards are shut, but there are still some twenty-five patients who are not encouraged to leave the ward without the nurse in charge being informed so that an escort can be provided if this is thought wise This number is, I think, higher than it should be, and can be further reduced

There are over five hundred female patients and they are now occupied in much the same varied way as are the male patients whose activities I described in an earlier article[1] The statement often made that lack of nurses is all that prevents a full and relatively free life for the patients of a mental hospital has been proved untrue by the fact that, even when the total number of female nurses of all grades on duty is twenty or less, the same varied day goes on

Last summer we were lucky enough to be able to hire a camp by the seaside

The conditions were reasonably good, though living was rather rough compared with the hospital There was room for sixty patients One ward was sent en masse, its patients being all schizophrenics in their middle 30s with an average stay in hospital of nearly ten years

They were looked after by the same nurses who cared for them in hospital, a van bringing the different shifts of nurses on duty The chief male nurse, a charge nurse, and a staff nurse lived at the camp for most of the time

There were several good results The patients enjoyed themselves, and showed it by their cheerful bearing and the willing way in which they worked at camp tasks Two schizophrenics whose antisocial habits and persecutory beliefs made their behaviour at the hospital rather suspect, turned to and worked so hard that on their return to the hospital they were found jobs in a hospital department—one of them has just left to take up a paid job Two other schizophrenics who normally showed little or no sign of interest in things began to talk, and this improvement has been maintained

Our local repertory theatre presents a new play each week, and thirty patients go to it (fifteen men and fifteen women) They are chosen from what in other days would have been called refractory wards, they all need considerable nursing care to keep them as well as they are, and they would not be able to remain well unless they were "grouped" for their ordinary day They behave well at the theatre

From another hospital we have adopted the idea of using a staff nurse to find work for long-stay patients who would not be able to find or hold a job in competition (There is no idea of using him to seek work for recently admitted patients, because the disablement resettlement officers do this quite well)

All we ask of the employers is that they should pay the patient a fair wage, look after him, and see that his other workers appreciate the situation, and I am glad to say that both employers and employed have been most kind and helpful Some of the work found has been for groups of up to eighteen patients, with nurses to help and supervise (I may mention here that our hospital owes much to its trade-union secretary, whose advice is always sought when fresh schemes of any sort are considered I wonder whether greater advances in mental hospitals would not be obtained if these secretaries were more generally consulted) A few patients have found what may be regular employment and are living out of hospital They know that if the job finishes they can come back to us until something else turns up A nurse regularly visits their place of work and lodging to make sure there is nothing that they want and that they are well looked after

All these patients have been in hospital for some years and are obviously psychotic, but as hospital care seemed to have produced all the improvement it was likely to, a change of this nature was clearly the next step in their programme of treatment

Another problem which we face in common with many mental hospitals is the patient with gross organic brain damage whose family would like to have him at home but who find his restlessness and occasional incontinence more than they can bear Here, once we and the family feel it is proper, we send the patient home and have him brought up every day, including Sunday Where necessary, a nurse calls at the house first thing in the morning to get a report and to do anything necessary to help the family This, of course, is more of a geriatric than a psychiatric task, but by helping these old people we also help the ward and the morale of the nurses When no serious effort is made to treat patients, the staff become discouraged, knowing that they have the patient until he or she dies The patient's relations also know that death is the only result of a stay in that ward

When patients are treated actively it is surprising what changes can be made in the most unlikely of them In this hospital, except the sick wards, all the wards with so-called long-stay patients are the direct personal responsibility of a consultant psychiatrist who has no junior colleague to help him, for we believe that consultant staff should do a large proportion of their work in those wards where the patients' illnesses present problems requiring special skills and experience

SUMMARY

Every advance may be the enemy of the next, and today there is a danger that open wards and voluntary patients will come to be regarded as an acceptable substitute for treatment

The psychiatrist must be able to change his methods, for often a technique which produces initial improvement will need modification if it is to continue to give good results

The wide scope for experiment in therapeutic techniques is illustrated by some which are at present proving useful for patients who have been in a mental hospital for many years

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[1] Bickford J A R Lancet, 1955, ii 969

Points of View

SOLDIERS AND LABORATORY ANIMALS *

An analogy for experimental biologists

MAJOR C W HUME
M C, B Sc Lond
SECRETARY-GENERAL OF UFAW (THE UNIVERSITIES FEDERATION FOR ANIMAL WELFARE)

AT the time of the battle of Paschendaele there was current a story about a general who earned for himself the nickname of "Plenty-more-men" It was said that on one occasion a staff officer remonstrated against the reckless way in which he was squandering his reserves, but got the reply "Oh, there are plenty more men, plenty more men" Whether this story is true or not, we can all think of some biologist or other who deserves the nickname "Plenty-more-animals", if not in our own country, then in some foreign country where funds for research are available *en veux-tu en voilà*

The analogy between a military commander who has to send his troops into battle and an experimental biologist who has, let us say, to ascertain an LD50 by some appropriate procedure is close enough to deserve consideration

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* Introductory paper read at the UFAW symposium on Humane Technique in the Laboratory An abstract has already appeared in the report of the symposium published as vol 6 of the *Collected Papers of the Laboratory Animals Bureau of the Medical Research Council*

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From the point of view of his superior officer, a soldier has two entirely different aspects, which I shall call respectively his "cold-blooded" and his "warm-blooded" aspects, and it is his superior's duty to take account of both In his cold-blooded aspect the soldier is a regimental number on the strength of a certain battalion When his battalion is sent into action he automatically goes with it The expected percentage of casualties will have been estimated in preparing the plan of battle, in other words, his chance of becoming a casualty is a cold arithmetical factor in a statistical calculation If he does become a casualty he is a detail to be deducted from the ration strength of his unit and accounted for in the parade state That is his cold-blooded aspect

A laboratory animal also has its cold-blooded aspect In this aspect it is just one of a sample of, say, ten, duly numbered in the records of the animal-house, it is one point on a regression line, one unit in a quantal response In evaluating the results of the experiment such details as its litter number, age, sex, genetic history, and physical response to a given procedure are all that is usually taken into account The fact that it has a personality is of no interest in this connection, the recorded data concerning it are similar in principle to those which are requisite in relation to chemical samples or reagents, or to the characteristics of thermionic valves in an experimental apparatus

So much for the cold-blooded aspect of soldiers and laboratory animals But each of these has a second aspect, which I have called the "warm-blooded" aspect

Let us take the soldier first It is a regimental officer's duty to know his men and to look after their welfare He must inspect their billets and concern himself with their comfort He must keep an eye on their rations and make a howl if these are unsatisfactory He must arrange recreation for them He must even attend, if necessary, to their private affairs, and do what he can for a man whose child is dangerously ill or whose wife has eloped with a stranger This is the soldier's warm-blooded aspect, and an officer who neglects it is being not only inhuman but also technically incompetent, because morale is of great technical importance and nothing is more destructive of morale than indifference to the fact that the men have human feelings as well as regimental numbers A divisional general cannot, it is true, know all the men under his command, but even he will try to see as much of them as he can and to understand their human problems

In the same way laboratory animals have a warm-blooded aspect, even cold-blooded animals like xenopus have one, metaphorically speaking A competent biologist will pay great attention to the housing, feeding, and health of his stock, and he will manage them in such a way as to avoid exposing them to any mental stress which is avoidable, he must keep them happy as well as healthy Failure to do this is inhumane, but it is also inefficient, because healthy and contented stock are an asset in any research, and the biologist who was indifferent to the feelings of his animals would to that extent be technically incompetent as well as callous The analogy can be pressed even further In the same way that comradely relations between higher and lower ranks in an army are essential to good morale, so a friendly relation between laboratory animals and laboratory staff keeps the animals tame and so makes them easy to handle and free from stress, besides rendering their short lives happy

A good biologist will, then, pay much attention to this warm-blooded aspect of the animals he uses, first because as a civilised being he will wish to behave in a humane way, and secondly, though only secondly, because it pays him to do so Humane management of laboratory animals makes for efficiency in research

* * *

Leaving the animal-house, let us now turn to the laboratory Many years ago, the late Prof E S Starling expressed to me the opinion that a good deal of the physiological research which was being done in a certain foreign country was being vitiated because the physiologists concerned did not trouble to eliminate pain, and so the secondary effects of pain were being confounded with effects of other conditions which these workers were trying to study

Dr W M S Russell has conveniently classified under three headings, which he calls the "three Rs," the considerations which bear upon the warm-blooded aspect of animals in the laboratory These headings are replacement, reduction, and refinement, and we can apply our military analogy to them

Here is an example of replacement

In the early days of the first world war, every infantryman carried a pair of pliers with which to cut the enemy wire by hand, and in carrying out this operation the infantry were mown down by machine-gun fire But later on, inanimate high-explosive shells were substituted for these living wire-cutters, and wire-cutting by the guns was a normal phase in every attack The replacement section of the UFAW symposium deals with the replacement of live animals by non-sentient materials such as micro-organisms, tissue cultures, and even electrical models in some cases

For Russell's second R, reduction, a military analogy can be found in the clearing of minefields

A man who served as a liaison officer with the Russians assured me that he had seen a platoon of infantry marched across a suspected minefield for the purpose of making it safe If this was regarded as an orthodox method the number of personnel required must have been high and the casualty-rate must have been heavy In any event, the use of mine-detectors makes possible a great reduction in the number of personnel

Ways of reducing the number of animals required for a given degree of precision include the methodological design of experiments and the control of variance by means of applied genetics and by paying attention to specific environmental factors

Dr Russell's third R is refinement of techniques for the purpose of reducing discomfort in cases in which discomfort cannot be wholly avoided

This refinement of experimental techniques finds a military analogy partly in the steps taken for preventing casualties (the provision of steel helmets and respirators, for instance), and partly in the field medical services—stretcher-bearers, regimental aid posts, field ambulances, casualty-clearing stations, and military hospitals These are concerned not only with the technical advantage of preventing casualties and getting lightly wounded men back into the line again, they are also concerned with the humanitarian purpose of easing the sufferings of men who are so severely wounded that they will never fight again This care for the severely wounded and the dying, though incidentally it has the technical advantage of improving morale, is primarily a humanitarian activity In the laboratory there may be cases in which no technical advantage is got by obviating pain in an experiment, no error introduced by allowing a rat or a rabbit to recover prematurely from an anæsthetic, but are not encouraged to leave the ward without the nurse in charge being informed so that an escort can be provided if this is thought wise This number is, I think, higher than it should be, and can be further reduced

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So much for the cold-blooded aspect of soldiers and laboratory animals But each of these has a second aspect, which I have called the "warm-blooded" aspect

Let us take the soldier first It is a regimental officer's duty to know his men and to look after their welfare He must inspect their billets and concern himself with their comfort He must keep an eye on their rations and make a howl if these are unsatisfactory He must arrange recreation for them He must even attend, if necessary, to their private affairs, and do what he can for a man whose child is dangerously ill or whose wife has eloped with a stranger This is the soldier's warm-blooded aspect, and an officer who neglects it is being not only inhuman but also technically incompetent, because morale is of great technical importance and nothing is more destructive of morale than indifference to the fact that the men have human feelings as well as regimental numbers A divisional general cannot, it is true, know all the men under his command, but even he will try to see as much of them as he can and to understand their human problems

In the same way laboratory animals have a warm-blooded aspect, even cold-blooded animals like xenopus have one, metaphorically speaking A competent biologist will pay great attention to the housing, feeding, and health of his stock, and he will manage them in such a way as to avoid exposing them to any mental stress which is avoidable, he must keep them happy as well as healthy Failure to do this is inhumane, but it is also inefficient, because healthy and contented stock are an asset in any research, and the biologist who was indifferent to the feelings of his animals would to that extent be technically incompetent as well as callous The analogy can be pressed even further In the same way that comradely relations between higher and lower ranks in an army are essential to good morale, so a friendly relation between laboratory animals and laboratory staff keeps the animals tame and so makes them easy to handle and free from stress, besides rendering their short lives happy

A good biologist will, then, pay much attention to this warm-blooded aspect of the animals he uses, first because as a civilised being he will wish to behave in a humane way, and secondly, though only secondly, because it pays him to do so Humane management of laboratory animals makes for efficiency in research

* * *

Leaving the animal-house, let us now turn to the laboratory Many years ago, the late Prof E S Starling expressed to me the opinion that a good deal of the physiological research which was being done in a certain foreign country was being vitiated because the physiologists concerned did not trouble to eliminate pain, and so the secondary effects of pain were being confounded with effects of other conditions which these workers were trying to study

Dr W M S Russell has conveniently classified under three headings, which he calls the "three Rs," the considerations which bear upon the warm-blooded aspect of animals in the laboratory These headings are replacement, reduction, and refinement, and we can apply our military analogy to them

Here is an example of replacement

In the early days of the first world war, every infantryman carried a pair of pliers with which to cut the enemy wire by hand, and in carrying out this operation the infantry were mown down by machine-gun fire But later on, inanimate high-explosive shells were substituted for these living wire-cutters, and wire-cutting by the guns was a normal phase in every attack The replacement section of the UFAW symposium deals with the replacement of live animals by non-sentient materials such as micro-organisms, tissue cultures, and even electrical models in some cases

For Russell's second R, reduction, a military analogy can be found in the clearing of minefields

A man who served as a liaison officer with the Russians assured me that he had seen a platoon of infantry marched across a suspected minefield for the purpose of making it safe If this was regarded as an orthodox method the number of personnel required must have been high and the casualty-rate must have been heavy In any event, the use of mine-detectors makes possible a great reduction in the number of personnel

Ways of reducing the number of animals required for a given degree of precision include the methodological design of experiments and the control of variance by means of applied genetics and by paying attention to specific environmental factors

Dr Russell's third R is refinement of techniques for the purpose of reducing discomfort in cases in which discomfort cannot be wholly avoided

This refinement of experimental techniques finds a military analogy partly in the steps taken for preventing casualties (the provision of steel helmets and respirators, for instance), and partly in the field medical services—stretcher-bearers, regimental aid posts, field ambulances, casualty-clearing stations, and military hospitals These are concerned not only with the technical advantage of preventing casualties and getting lightly wounded men back into the line again, they are also concerned with the humanitarian purpose of easing the sufferings of men who are so severely wounded that they will never fight again This care for the severely wounded and the dying, though incidentally it has the technical advantage of improving morale, is primarily a humanitarian activity In the laboratory there may be cases in which no technical advantage is got by obviating pain in an experiment, no error introduced by allowing a rat or a rabbit to recover prematurely from an anæsthetic, but nevertheless the moral obligation to conduct research with a minimum of pain, fear, and stress is a binding one.

* * *

Believing this military analogy to be genuinely relevant, I will add one final point. No military commander is entitled to subject his men to risks and sufferings which he himself would *not* be prepared to endure if, *mutatis mutandis*, circumstances required him to do so. I say "*mutatis mutandis*", and in particular let us, in the laboratory analogue, leave aside the risk of death, because this is irrelevant when one is going to compare animals with human beings; let us consider only exposure to pain, discomfort, or stress. We may bear in mind also that circumstances do not ordinarily require a divisional commander to expose himself to the same risks as the front-line troops, however often he may have done so in his younger days; his duty is now different from theirs. But in principle he ought to be ready to face anything he calls upon them to face. If we turn now to the biologist, we may say that only in rather exceptional cases can he usefully subject himself to experimental procedures in the laboratory, though a number of research-workers have done this from time to time. On the other hand, he may usefully ask himself whether, if he were this or that experimental animal, he would be willing to make voluntarily the sacrifice which he is calling on the animal to make, for the sake of the purpose for which the experiment is to be performed, apart always from any question of life and death, and account being taken only of any pain, discomfort, or stress that may be entailed.

Public Health

Antioxidants

THE nutrition panel of the food group of the Society of Chemical Industry met on Dec. 11 to discuss antioxidants.

Dr C. H. LEA said that many unsaturated compounds, particularly fats and related substances, oxidise spontaneously in air and become rancid. This autoxidation is a chain reaction. The addition of antioxidants is one of several means by which undesirable oxidative changes in fats or fat-containing foods can be combated. Antioxidants are of two types—the primary chain breakers (usually phenols) and the synergists, which probably function by inactivating the traces of catalytically active metals present in many autoxidisable materials.

Primary chain breakers which may be used in limited quantities in certain classes of foods include propyl, octyl, and dodecyl gallates, butylated hydroxyanisole (B.H.A.), and butylated hydroxytoluene (B.H.T.). Aromatic amines, which are used in petroleum and rubber technology, are not usually permitted in food, because of a tendency to cause discoloration and of doubts concerning their harmlessness. An important potential use of antioxidants is for the protection of vitamins A and E and of carotene in animal feeding stuffs.

Often a mixture of antioxidants is better than a single substance: a synergist (e.g., citric acid, ascorbic acid, or polyphosphate) may be essential if trace-metal concentration is high. No clear dividing-line exists between the two groups of antioxidants; for instance, the flavonol gossypetin can function both as a chain breaker and as a metal deactivator.

Antioxidants are in general more effective in improving the stability of animal than of vegetable fats, because the latter are already rich in natural antioxidants. They can be used to stabilise fats and oxidisable colours, flavours, and vitamins in foodstuffs. Ascorbic acid, particularly when traces of copper are also present, can accelerate the development of rancidity, whereas under other conditions it can be a useful antioxidant. Antioxidants can sometimes be produced in the food itself by heating, as in the application of high-temperature preheating in the manufacture of whole-milk powder.

Mr R. J. WARD said that of the synthetic antioxidants butylated hydroxyanisole and butylated hydroxytoluene are quantitatively the most important, followed by the gallates and, to a much lesser extent, nor-dihydroguaiaretic acid (N.D.G.A.). The tocopherols are probably the most important natural antioxidants.

Extraction of petrol solutions of fats with water, aqueous ammonium acetate, methanol, and aqueous ethanol has been used to separate the gallates, N.D.G.A., and B.H.A., but B.H.T. cannot be separated quantitatively by this method. Steam distillation has been used to separate B.H.A. and B.H.T. from fats, and column chromatography on silicic acid has been used to isolate B.H.T. from fats. After preliminary purification the tocopherols are separated on a two-dimensional paper chromatogram employing adsorption and reverse-phase chromatography. Colour reactions are used for the estimation of all the antioxidants, and a spectrophotometric method for B.H.T. has been described. Paper chromatography has been used to identify antioxidants, but so far not for their quantitative estimation.

In assessing the suitability of antioxidants for use in food, account must be taken of both acute and chronic toxicity in more than one species of animal, of which one should be a non-rodent. An antioxidant is considered harmless if the LD$_{50}$ value is 1000 mg. per kg. or more, and if feeding at a hundred times the level used in food does not depress growth. The gallates and B.H.A. are relatively non-toxic, but B.H.T. shows normal growth at the 0.8% level and some growth depression at the 1% level. Compounds exhibiting a sharp cut-off in this manner are usually found to be harmless, and, as B.H.T. shows no other toxic effects, it may be used as an antioxidant.

Home Accidents and Local Authorities

It is becoming accepted that prevention of accidents in the home comes within the scope of the local health authorities, and a circular (6/58) from the Ministry of Health draws attention to the part they can play. With the circular was distributed a memorandum, entitled Accidents in the Home: Burns and Scalds, which says that about 700–800 people die from this cause in England and Wales each year, and about 50,000 are treated in hospital for burns. About 80% of the fatal burns are due to ignition of the patient's clothing. The memorandum gives advice on prevention, with information about fireguards, location of heating appliances, inflammability of clothing (a British standard is to be published soon), and kitchen techniques to prevent scalds. The information should be of particular use to health visitors and other social workers, and to all conducting child-welfare clinics.

Hygiene in Canteens

The National Coal Board is to be congratulated on its brief memorandum setting out simply and clearly for laymen the things that matter in the prevention of food-poisoning in canteens.[1] Three objectives are stated: (1) within the canteen itself, bacteria should not be added to the food, (2) food within the canteen should not be left in conditions that favour bacterial growth, and (3) cooking should be adequate to kill bacteria in the food. Photographs and diagrams admirably illustrate a good text and show exactly how the three objectives can be realised. The booklet contains nothing that is unfamiliar but a great deal that appears to be almost systematically neglected. Canteen managers who wish to reduce their own contribution to the incidence of food-poisoning will study the advice contained in three sentences on p. 13:

> "The surest precaution against food poisoning is to cook food thoroughly as soon as possible after receipt and to serve it immediately thereafter. This applies particularly to those food, especially meat, which readily permit the growth of bacteria. If there is an appreciable interval between the receipt and serving of such foods, it is preferable to keep them in the refrigerator and to cook them immediately before serving rather than to cook them, refrigerate them, reheat, and then serve."

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[1] Medical Memorandum no. 1: Hygiene in Canteens. 2nd ed. 1957. Published by the National Coal Board, Hobart House, Grosvenor Place, London, S.W.1.

In England Now

A Running Commentary by Peripatetic Correspondents

So many breakfast cereals are now constructed to make noises when the milk is added that if my deaf-aid has broken down I can't tell what I'm eating Our latest one goes 'Crunch! Crackle! OUCH!', these last two noises being made by the disintegration of one's dentures under collision with the glass marbles and small plastic toys with which the manufacturers lace their product in order to overcome consumer-resistance They could well throw in a tracheotomy tube or two for consumers whose resistance is being overcome by asphyxia due to tracheal obstruction

The consumers' death-rattles arouse no sympathy in the "Famous Old Sea-dogs of Fact and Fiction" whose portraits are on the packet—callous characters who subsisted entirely on rum and who had therefore no use for teeth except for carrying cutlasses All over the packet are cajolements and commands about applying for other "free" gifts, and today, as I spooned morosely around amongst the plastic tokens of the manufacturers' esteem on the off-chance of finding something to eat, I thought that the manufacturing chemists really let us off pretty lightly Supposing their advertisements went all cornflakery

> Doctor! This Hi-fi autoclavable stethoscope FREE for only twenty-five bottle-tops from 'BHANG' the NEW Tranquilliser, and a postal-order for 1*s* 9*d* BHANG! BHANG! Makes your patients bite the dust!
>
> Your initials and qualifications engraved FREE on each set of hand-tooled genuine pseudo-Georgian percussion hammers given away with every gallon of Mist. Mescalyn Co, the medicine that enables you to see T V better with the set switched off

And for the kiddies, capsules shaped like I C B M s and sputniks, which during assimilation go Bleep! Bleep! on 108 megacycles No consumer-resistance could withstand that sort of thing, and the Great British public would be into our surgeries so fast we should have to bank the curves in the garden-path

Incidentally, one citizen who really enjoys his crepitating breakfast-food is Ananias' cousin Fred, who depends on it for his annual holiday He has a large helping and rushes off to have his chest sounded The stethoscopic atmospherics over his left base are so extraordinary that they earn him at least two weeks' free board and lodging in any chest clinic in these islands

* * *

The other day I was told that the way of life reflects the mode of birth Since then I have been thinking about the ways of life of those friends and colleagues whose method of delivery I happen to know For instance, I have felt more tolerant towards a tiresome female colleague since I realised that she persistently reverses the work of others because she was born as a breech Another colleague, who has to be dragged with the greatest moral force before he can be induced to perform his duties, is the proud possessor of the forceps which delivered him A small boy whose mother says he gives her fits because of his delight in the hazardous reminds me of the night before his birth when I had to cope with his mother's eclampsia

Of course, I know the birth details of only a few of my colleagues, and this has provided me with an amusing game I feel sure that my friend who has failed his M R C P for the eighth time was the result of a prolonged labour, and a contemporary whose meteoric rise to the top of the profession left the rest of us gaping must surely have been a B B A The youngest man in my year, who won all the prizes and the university medal, and then developed normally as a G P, was, I feel sure, a prem How many registrars struggling for existence suffered from fœtal distress?

The circumstances of my own birth give me food for thought I was born by cæsarean section performed for obstructed labour I can, however, find nothing in my life that reflects this dramatic event Maybe this is because the operation was in fact performed for my brother (and the less said about his career the better) I myself was the undiagnosed twin lurking in the background, which of course accounts for the pleasure I take in writing anonymously as a peripatetic correspondent

* * *

In 1949, in the early days of our group for congenital heart-disease, we saw a blue but otherwise bright young girl of 22 with the cheerful name of Joy We thought she had Fallot's tetralogy and performed a Blalock-Taussig anastomosis with great benefit to her health, energy, and colour It was not long before she was inquiring about the advisability of pregnancy, for she was about to be married In our wisdom, and obsessed with the fear of transmission of defects, we thought she should not become pregnant, and sent back word "Let Joy be unconfined" That was in 1950 She married happily, and in 1955 *she inquired again* Our views had changed, and we advised then that Joy might be confined She was, to the satisfaction of all concerned, and came to see us last week with a fine infant of 7 months The next question was whether she should confine her confinements to one But enough of this

* * *

Johnny was a bright young lad rising 5 years old and his mother gave him 3*d* to buy some sweets, and that was when we met, because the sweetshop lay across the road and in eagerness to get his hands on a quarter of dolly mixtures he rushed all unaware from behind a parked van straight into my front bumper I lifted him screaming from the gutter and a crowd quickly gathered including, happily, Mum Our hospital lay not a hundred yards distant and I soon had him lined up in front of the cathode-ray tube within the hour his battered femur was straightened and safely plastered Father was a lorry-driver and knew his rights "Show me the doctor what done it," he said, but I was collecting statements from the lady in the sweetshop who said it was a disgrace and the police oughtn't to allow that van to park there, and the gentleman next door who saw it all, so that when father's insurance assessors sent in their claim my company were able to send them "an appropriately worded reply" and the matter has been laid to legal rest

It remained, however, for the ultimate indignity to be heaped upon me My own dear Miss Flitt, our almoner, who has time and time again given solace when social problems oppressed sent me a bill for 10*s* 6*d*, and what's more she sent it registered She said that under the Road Traffic Act of 19 something-or-other our hospital had been the first to render aid and would I kindly pay this sum or else When I tackled her that afternoon she said she was sorry but they always did that for Road Accident cases, would I see the finance officer? I told the finance officer that I resented paying the hospital for services rendered by myself in my own time indeed the very first assistance of a medical nature had been rendered by me in the road nowhere near his silly hospital He said it did sound odd but would I please pay because if it got into the hands of the lawyers it just might never end I said I'd see him in hell first, and, for the first time in years, called out the might of one of our Great Professional Institutions it rose magnificently to the occasion and told me hair-raising stories of casualty officers who, after applying a little of their own gentian-violet to a graze sustained in climbing aboard their *motor-cycle*, were sent this silly little registered demand They too sent "an appropriately worded letter" and all I ever get from the finance officer now is a very dark look

* * *

"rocket, n Kinds of plant of which some are used as salad & some grown for flowers (*Base r*, wild mignonette, *Blue r*, kinds of wolfsbane & larkspur, also bluebell)"—*Concise Oxford Dictionary*

A rocket by a river's brim
A kind of plant it was to him,
And it was nothing more
And how contented I should be
If that was all it was to me.

Letters to the Editor

SEPTIC SURGERY

SIR,—Your timely and most valuable leader (Feb 8) on the relationship between operative infections and operating-theatre discipline prompts a reflection Are standards of theatre discipline laxer today than they were twenty-five years ago, especially as they concern dress, footwear, theatre traffic, and baths by surgeons?

Certainly when I was a ward clerk, my first surgical registrar (now a consultant on the staff of his hospital) would, in the most silent and astringent manner possible, have blasted me from any theatre in which I appeared without goloshes over my shoes, nor would there have been anybody present in any theatre at that time with outdoor footwear uncovered How often is this so today? How often in fact do surgeons change completely, at least for single operations? How often do they take baths before or after operations today? My memory of my chiefs in the 1930s is that they were always popping in and out of showers Today many theatre suites, even those built since the war, are quite scandalously without shower facilities Indeed, the changing-room accommodation in many is reminiscent of the changing-room at the old Ring, Blackfriars, on the Hospital Boxing Championship night, when all weights from all nine teaching hospitals had to change, sweat, and bleed, before, between, and after bouts in a room about 8 ft × 8 ft, in atmospheric conditions not very dissimilar to those of some surgical changing-rooms of today How often also do surgeons, and theatre staff, plan the traffic in theatres during operations, and take steps to limit it?

I know that I am a frequent offender against many of these necessary rules for the limitation of airborne and indeed contact infections in theatres

It is easy to appreciate that some decline in the level of the technique and the theatre discipline, which was brought to perfection in the Lister to Lane epoch, was inevitable, as the risk of theatre infection became less in frequency and in severity, but your leader reminds us, if reminder is necessary, that theatre infection is still a major problem in surgery I wonder if my belief, that standards of theatre discipline are laxer than twenty-five years ago, is right If this is so, does it mean that surgeons today do not in fact agree that the high theatre discipline you describe is necessary?

London W 1 **PATRICK CLARKSON**

SIR,—Your leading article is timely and may stimulate into activity those who can reduce the incidence of cross-infection

Some of the changes suggested at the symposium organised by the Association of Clinical Pathologists are expensive and therefore cannot be implemented immediately or even within the next few years That is no reason why many useful, simple, and cheap measures should not be taken now to reduce cross-infection

The real trouble at present is that far too many consultants pay only lip service to the problems of cross-infection It is very much against the interest of the patient for surgeons to leave the theatre to visit a ward or casualty to see an urgent admission while still wearing theatre robes and with their masks around their necks It is all too easy in this way to disseminate bacteria from the nose and throat via the hands to the patients It is equally easy to take back bacteria from casualty on their dressing-gowns to the theatre

The present high incidence of troublesome resistant bacteria calls for a real appreciation of the risks taken by senior staff themselves who must set an example to their juniors

Such problems, of course, are particularly apt to arise when surgeons' admitting days coincide with their elective lists, and perhaps they should review their present programmes

Central Middlesex Hospital,
London, N W 10 **J D ALLAN GRAY**

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—I have been interested to note that the pioneer work which I carried out 14 years ago in Oxford on the use of monofilamentous nylon for surgical sutures[1] has been followed by further studies by others there[2 3] They confirmed my findings that even in the presence of sepsis wound healing progresses rapidly and without extrusion of the sutures A chronic sinus following the use of the finer (nos 3 to 5) sizes of monofilamentous nylon is almost unknown in my experience of many hundreds of cases However, I have seen several such sinuses when the surgeon had used the thicker sizes, and I believe that the incidence of chronic sinuses is related to the amount of the suture material buried But I have found a much higher incidence of chronic sinuses, requiring removal of the sutures, when multifilamentous material, such as silk, linen thread, braided nylon, or (worse still) braided 'Terylene' ('Mersilene'), was used, and certainly my investigations show that there is a much higher incidence of wound infection if catgut is used I think it fair to claim that monofilamentous nylon gives less trouble from infection than the other suture materials in common use, and from this standpoint it is not at a disadvantage as Mr Marsden (Feb 15) suggests

Nevertheless, it has two main disadvantages one of which is its loss of tensile strength during storing and sterilising (I have encountered some specimens which snapped with a very slight pull) and the other is the loss of up to 75% of its tensile strength at the site of a knot This last figure is derived from my own tests with a tensometer This loss of tensile strength may not be important in a "darn" operation where no great stresses are to be expected, but it is a serious drawback in median or paramedian abdominal wounds, and it seems likely that one or other of the more recent synthetic fibres will prove more satisfactory in this regard at least

Like Mr Moloney (Feb 8) I continue to use monofilamentous nylon for hernia repairs, but like Mr MacLeod (Feb 15) I restrict the repair to suturing the fascia transversalis at the deep inguinal ring except when the muscles and fascia are very stretched and thin

Manchester **HERBERT HAXTON**

SIR,—There must be very many surgeons and registrars who, having spent a good deal of time removing pieces of monofilamentous nylon from the depths of chronic sinuses and recurrent herniæ, will feel reluctant to accept Mr Moloney's conclusions as to its suitability for hernia repairs If a nylon darn is the method preferred, surely floss nylon is far closer to the ideal material

Oldchurch Hospital,
Romford Essex **V B SETH-SMITH**

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1 Haxton H *Brit med J* 1945 i 12
2 Moloney, G E, Gill W G, Barclay R C *Lancet* 1948 ii 45
3 Moloney, G E, Russell W T, Wilson D C *Brit J Surg* 19[illegible] 38 [illegible]

SUBURBAN NEUROSIS UP TO DATE

SIR,—Dr Barrett, in his comment (Feb 1) on your leading article of Jan 18, suggests that the high incidence of psychoneurosis in the housing estate which we studied may be at least partly attributable to the fact that the population of such an estate is, in effect, selected for social incompetence They are families, he suggests, who were rehoused either because they were homeless or because they were living in insanitary conditions, and had been unable to find suitable accommodation by their own efforts

Unfortunately, Dr Barrett's account bears little or no relation to the criteria of selection which were in fact employed by the London County Council During the war years many thousands of London homes had been destroyed by bombing, no new houses had been built, and many new families had been founded As an inevitable result, there was considerable overcrowding in London immediately after the war, and it was to abate this overcrowding that the estate in question, together with several others, was developed Only 4% of the families on the estate had been living in rest centres before rehousing, and 13% had been living in insanitary conditions For the remainder, the explicit criterion of selection was overcrowding, supported in some cases by ill health In practice, a number of factors combined to ensure that the families who went to live on this estate were drawn from the upper levels of the working-class, with incomes well above the average of applicants for London County Council housing, and with excellent rent records We know of no evidence which might suggest that such families have any special predisposition to mental illness

Department of Public Health and Social Medicine,
University of Edinburgh

J H F BROTHERSTON
F M MARTIN
S P W CHAVE

A PLASTIC APPROACH TO SURGERY

SIR,—Mr McGregor (Jan 25) took me up on the advocacy of the use of Langer's lines Obviously we differ in the meaning of this expression Unless we have the same experience, even the meaning of words can differ, and more so the meaning of a scientific paper To me Langer postulated lines on the body along which, if we made our incisions, optimum scarring resulted These lines vary from person to person and age to age and no diagram can represent them, Langer's diagrams represent his findings in certain cases based on the circular stab method To show how age affects the change of direction, almost any incision for the block dissection of glands of neck in the aged will give a good scar, whereas the chubby young thing with a thyroglossal cyst will get a horrible scar if we deviate from the transverse incision which happens to lie parallel with the crease line The difficulty is to find the Langer line for each particular case, or should it in future be called the "Heanley" line?

Mr McGregor quotes Kraissl[1] who in turn quotes Ferris Smith "Much that has been said about the value of incisions in these lines is true and desirable, but the conviction that incisions across these lines invariably produce bad scars is not correct" I remember a meeting on Dupuytren's contracture at the Royal Society of Medicine in which a discussion of the best incisions in the palm cropped up, and the conclusion was that the best incision was transverse in the distal palm I was by the door and the porter said "Them doctors know nothing, look at my hand" He had a beautiful result from a Dupuytren's, and a longitudinal incision had been used I think we must accredit to Langer these lines of optimum incisions, although his diagrams are not of universal application, and we may not agree with the methods by which he worked them out Previous to Langer, incisions had for the most part been advocated either to avoid the cutting of cutaneous nerves, or for the ease of approach, with no contemplation of the eventual scarring

London, E 1

CHARLES HEANLEY

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[1] Kraissl, C J Plast reconstr Surg 1951, 8 1

RETURNS FROM MASS-RADIOGRAPHY UNITS

SIR,—Mass-radiography units have recently been informed of a new method of statistical returns to the General Register Office The changes are presented as "simplifications", but they are unlikely to be received with great enthusiasm by the staff of M M R units, who by now have become efficient in using the system introduced in 1954 From the purely administrative angle, it is for instance difficult to see why the old code numbers could not have been retained for the same groups of diseases in the abbreviated list of conditions which have now to be reported to the Registrar General

More important, however, "simplification" is a remarkable understatement with regard to the epidemiological information in which the authorities are now interested It is true that notifications of tuberculosis are only a crude epidemiological measure, but the Ministry of Health uses them as the basis of all tuberculosis statistics Mass-radiography units are no longer asked to report the number of their cases which have been notified, and the contribution of M M R to case-finding, which has been gradually increasing year by year, will from now on be an unknown quantity Similarly, the number of infectious cases found by M M R, and therefore its contribution in emptying the "unknown-infector pool", will fail to be recorded

This is not to say that the previous system was faultless, but it allowed statistical evaluation of very considerable epidemiological importance Some time ago I had the pleasure of reviewing[1] Dr V H Springett's excellent monograph *Minimal Tuberculosis Found by Mass Radiography* Dr Springett's scheme of classification of tuberculosis was quite obviously the basis of the system now discarded by the Registrar General In my review, I expressed the hope that in future the interpretation of the large number of tuberculous lesions found by M M R would be entrusted to a mind not less competent than that of the author of this book Now it will hardly be worth anybody's time and trouble to analyse the scanty material available under the new system

With regard to non-tuberculous conditions, it may suffice to give a short list of conditions the Registrar General is not interested in bronchiectasis, spontaneous pneumothorax, metastases in the lung and mediastinum, bacterial and virus infection of the lungs

Who decided the changes and why were medical officers of M M R units not consulted as they were before the introduction of the previous code in 1954? These ill-considered changes seem to be purely a matter of misplaced administrative expediency

Mass Radiography Service,
Stoke-on Trent

E POSNER
Medical Director

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[1] Posner, E Brit J industr Med 1957, 14, 38

TREATMENT OF BREAST CANCER

SIR,—The "strong challenge from the Mayo Clinic" mentioned in your leading article (Feb 1) must not be taken too seriously by those seeking the correct management of breast cancer, for the published figures[1] can be shown to be entirely in accord with experience at other centres

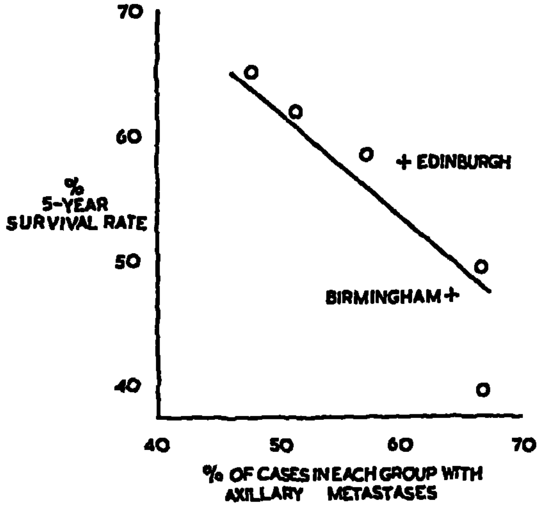
Study of the Birmingham series of patients with breast cancer[2] treated between 1936 and 1949 convinced us that the dominating factor influencing the five-year survival-rate was the state of the axillary nodes, 67 1% of those without node involvement and 31 6% of those with, reached their fifth anniversary Between these extremes there appeared to be a strict correlation of five-year survival and the proportion of cases with axillary-node involvement in any group

PUBLISHED FIGURES OF MAYO CLINIC

Period	Proportion with axillary metastases	5-year survival rate of all cases treated during the period
1910–24	66·6%	40 1%
1925–34	66 4%	49 5%
1935–44	57 0%	58 6%
1945–49	51 2%	62 0%
1950–54	47 6%	65 1%
Total	59 1%	52 1%

Overall survival-rate, patients with no axillary metastases	78%
Overall survival-rate, axillary metastases present	36 2%

The published figures of the Mayo Clinic provide the accompanying table, and are expressed graphically in the figure



Five-year survival-rates and proportion of cases with involvement of axillary nodes

A regression-line shows a remarkable correlation between the five-year survival rate and the proportion of cases in any period with axillary-node involvement

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Department of Radiotherapy,
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W H BOND
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[1] Berkson J, Harrington S W, Clagett O T, Kirklin J W, Dockerty M B, McDonald J R *Proc Mayo Clin* 1957 32, 645

[2] United Birmingham Hospitals Annual Cancer Report 1957, 3 1

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To take the second first, clinical medicine has long been based on the twin pillars of a *thorough* clinical history and an equally *thorough* clinical examination Laboratory investigation has lately been added It will be to the detriment of medicine if this third be allowed to supplant rather than support the two older pillars The history of infectious diseases indeed shows how well these have served us, for it was by clinical observation that, for example, Sydenham described measles, Heberden chickenpox, and Pfeiffer glandular fever Even today we still rely on them for our diagnosis of the first two, and how rarely do they fail us! Contrariwise there have been occasions when the laboratory had hindered rather than *helped* our understanding—e g, suggestions that Pfeiffer's bacillus, Barger's bacillus, and *Listerella monocytogenes* caused influenza, ulcerative colitis, and glandular fever respectively

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Does he appreciate, for instance, how far his "modern concept" of mental deficiency as a "social incapacity" differs from the ordinary member of the public's concept of mental deficiency—as something based solely on defect in intelligence?

Does he appreciate the basic tenet of public relations that, to get wholehearted public support and cooperation in the implementation of legislation, it is necessary for this first of all to be in intelligible form and secondly to be explained in easily understood form?

If the community gives powers over the liberty of the individual, it feels itself entitled to understand why it is giving them The necessity for such explanation does not seem, unfortunately, to have been appreciated in the working of the Mental Deficiency Acts and the present position is a sorry example of the misunderstanding that ensues

It is extraordinary that, in all the debates before both the 1913 and 1927 Acts, and the discussion on mental defectiveness that accompanied them in Parliament, there appears no definition of "mind"—this was left to the experts, the medical profession They have to date not made a particularly good job of it, for the course of events of which Dr Heaton-Ward complains shows that a negative definition—a declaration that "defect of mind is not of necessity defect in intelligence"—does not suffice It immediately, and not without reason, arouses the suspicion of those whom he terms "the 'Civil-Liberty' Guards"

Till now, this interpretation of the law has worked by virtue of the fact that the lay public in general and Parliament in particular (as was obvious in the recent debate on the Royal Commission's report) did not understand what was being done This state of affairs is now, however, altering There are three main reasons for this, all of which, it seems to me, must be understood if Dr Heaton-Ward's anxiety is to be relieved

The first is that the medical profession, in exercising its prerogative as to the definition of mental defect, did not appear itself to grasp that it was dealing with two quite separate conditions that the "social incapacity" of the so-called "feeble-minded" patient is something entirely different from the defective intelligence of the mentally subnormal, and consequently needs treating differently and in difference circumstances A mental-deficiency expert for instance, understands the reasons for an honours B A being found as a detainee in a mental-defective colony but the general public do not, nor, as a matter of fact, do I

The second is that, just as patients differ, so do doctors Certifying doctors have shown differing opinions as to what they regard as social incapacity to an extent which has, on occasions, defied the common sense

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A Merchant Navy officer, aged 54, had penicillin dermatitis after a course of penicillin injections four years ago Last summer he tried a Swedish milk diet and developed dermatitis of the face and arms, which was thought to have been caused by detergents He improved slowly on prednisone while in hospital in Belfast, but relapsed on returning home and was referred to me with a severe generalised exfoliative dermatitis

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[2] Alexander, M B Benjamin B, Maslen, L G C, Roden A T *J Hyg*, Camb 1952 50 261

[3] Giles C, Sangster G *J Hyg* 1948 46, 8

TREATMENT OF BREAST CANCER

SIR,—The "strong challenge from the Mayo Clinic" mentioned in your leading article (Feb. 1) must not be taken too seriously by those seeking the correct management of breast cancer, for the published figures[1] can be shown to be entirely in accord with experience at other centres.

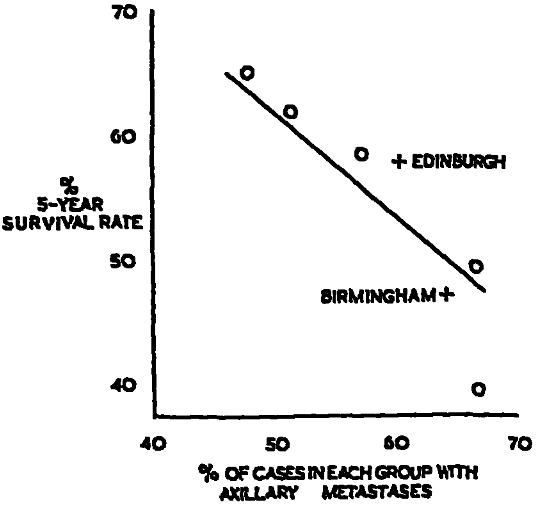
Study of the Birmingham series of patients with breast cancer[2] treated between 1936 and 1949 convinced us that the dominating factor influencing the five-year survival-rate was the state of the axillary nodes, 67·1% of those without node involvement and 31·6% of those with, reached their fifth anniversary. Between these extremes there appeared to be a strict correlation of five-year survival and the proportion of cases with axillary-node involvement in any group.

PUBLISHED FIGURES OF MAYO CLINIC

Period	Proportion with axillary metastases	5-year survival rate of all cases treated during the period
1910–24	66·6%	40·1%
1925–34	66·4%	49·5%
1935–44	57·0%	58·6%
1945–49	51·2%	62·0%
1950–54	47·6%	65·1%
Total	59·1%	52·1%

Overall survival-rate, patients with no axillary metastases	78%
Overall survival-rate, axillary metastases present	36·2%

The published figures of the Mayo Clinic provide the accompanying table, and are expressed graphically in the figure.



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The patient recalled reading in a Sunday paper of penicillin being fed to cows "to improve milk yield", and wondered, in view of his recent milk diet, if his previous penicillin allergy could have any bearing on his present rash

The Sunday paper concerned referred me to the source of their information, and it appeared that as much as 0 06 units of penicillin per ml could occur in samples of bulked milk or cheese

Dr Vickers has indicated that a much smaller amount can cause reactions in a penicillin-sensitive patient, and it seems highly probable that minimal quantities of penicillin persisting in bulked milk-supplies might be the cause of refractory allergic dermatitis more frequently than has hitherto been recognised

London, W 1 DAVID ERSKINE

THE TREATMENT OF PARAPLEGIA

SIR,—The entrance of a London hospital bears, I am told, the words "Curare, cito, tute, et jucunde" This is the essential aim of every hospital Even when a cure cannot be effected but the patient can be kept alive and reasonably well, the same principles apply Great success is achieved if such a person, though disabled, has a long and useful and happy life, especially if he does not require continuous medical supervision and frequent examination and investigation Such was my good fortune after my attack of paraplegia 27 years ago, and the simplicity of the methods of treatment during the first year, together with the freedom and independence I enjoyed during the next 25 years, form a striking contrast to the complex methods in use today

These methods, as practised with expert urological skill and care in the Liverpool Regional Paraplegic Centre, have recently been described [1] The routine initial treatment includes

1 Turning the patient in bed every 2–4 hours
2 A high fluid intake, 6 pints in the 24 hours
3 Prevention of pressure sores
4 Passive movements by physiotherapist
5 Transfusion of several pints of blood
6 Early ambulation

Mr Cosbie Ross and his colleagues describe a special method of treating the retention of urine with small-bore polyethylene catheters They also regard it as essential that the patient, even if free from symptoms, should continue to report regularly for the rest of his life and be admitted for a few days for clinical investigation, the estimation of residual urine, and excretion urography They write from wide experience, but it is interesting to compare their methods with the simpler ones successfully employed in my own case My illness was not traumatic in origin, but the same principles apply

My paraplegia occurred suddenly and quite unexpectedly, developing during 12 hours, on the 33rd day of a septicæmia, from which I was well on the way to recovery I had become very thin, and as a precaution against a bedsore had been placed on a waterbed 2 days before After the onset of the paraplegia, I lived on nothing but water and oranges for 10 days This was by my own desire, and seeing that my death was expected daily there seemed no reason why my invalid whim should not be gratified I became so emaciated that it was greatly to the credit of my nurses that no bedsore developed My pressure points were attended to every 2–4 hours and I was turned from side to side This turning also prevents stasis of the body fluids and reduces the likelihood of stones forming in the kidney It was carried out not merely in the initial stages but throughout my illness As soon as movement returned to my legs, my sleep was seriously interfered with by intermittent jerks or kicks, and it was found that if I were turned on my side (sometimes with cooling of my legs) I obtained at least half an hour's sound sleep Often I was turned from side to side as many as ten times a night This did away with the need for hypnotics—a point of great importance

My belief in the great value of *very* frequent changes of the position of the paraplegic patient from one side to the other was much strengthened during a visit, in 1949, to Dr L Guttmann's clinic at Aylesbury He showed me a photograph of a very large bedsore of the sacral region and buttocks in a paraplegic patient As soon as the patient was admitted, Dr Guttmann gave strict orders that he was to be turned from one side to the other, whether he was asleep or awake, *every half-hour*, day and night Photographs, taken weekly, showed rapid diminution in the size of the ulcer, and it was healed in six weeks Dr Guttmann thought that the type of dressing mattered little, but the changes of position were essential

The quantity of fluid taken was left to myself, and I kept it low in order to avoid the trouble of frequent catheterisation The catheter was passed twice in 24 hours, rarely thrice After the first distension (to 3 pints) it was passed whenever I asked for it, and this was consistently when the bladder had filled up to 14 or 15 oz It was never allowed to become distended above this level, or thereabouts When the catheter was discarded after about 5 weeks, the urine was very thick from a coli infection The bladder was washed out daily under gentle pressure An automatic bladder with small content rapidly developed, and then (except for one fortnight when an attempt was made to cleanse my bladder by washing out) no catheter was passed for 25 years

My lower limbs were moved by the nurses until the advent of the physiotherapist, 4 weeks after onset He also massaged my legs for a complete hour, daily, 7 days a week I believe that the massage helped the circulation, the nutrition of the muscles, and my metabolism and that the frequent changes in position (preventing stagnation of the body fluids), together with massage, are as good a substitute for active exercise as a bedfast patient can have, and should be continued, gradually modified, until full ambulation The extra tax upon the nursing staff and the physiotherapist at the beginning is fully rewarded later When I got up for the first time, precisely 3 months from the onset, I was able to walk to and fro in front of the fireplace, steadying myself by holding on to the mantelpiece Early ambulation was not artificially hurried

I had no blood-transfusion and did not seem to suffer from the want of it

10 months after the onset of my paraplegia, I returned to my work as honorary surgeon It came about in this way The late Dr George Riddoch, whose eminence in this department of medicine was beyond question, had examined me and considered my case *carefully* He had before him my history and notes of the clinical examination, cystoscopic examination, residual urine, and bacteriological examination of the urine His verdict was to this effect "You must return to your work on Jan 1 It is an order I expect that after some months you will be able to carry out your full duties as honorary surgeon to Bradford Royal Infirmary to the end of your term of office (10 years)" He gave me no instructions about supervision Happening to be in London, I called to see him twice during the next 3 years Dr Riddoch's dogmatic reassurance, when he sent me back to work, and the absence of supervision set me free from invalid and morbid feelings and gave me a much-prized independence for 25 years My mode of life has been described elsewhere [2]

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[1] Ross, J C, Gibbon, N O K, Damanski, M *Lancet*, 1957, ii, 520

[2] *ibid* 1956, ii, 35

At the end of 25 years my health began to fail I thought this was due to old age (75) My urological surgeon had often warned me that a urinary obstruction was likely to develop in later years And so it turned out My blood-urea rose in less than 3 months from 63 to 158 mg per 100 ml I was given the option of an indwelling catheter for a time or an immediate suprapubic cystotomy I chose the latter Performed under local anæsthesia, it was attended with immediate success, and there has been no leakage whatever My nutrition and general health quickly returned to normal, and my blood-urea is slowly falling There will be no need for further investigation to find if the cause of obstruction is an enlarged prostate or a pathological state of the bladder neck, for I am comfortable, active and mobile, and content

Simplicity has been the keynote of treatment in the above case There was no blood-transfusion, and no excess of fluid was given Emphasis was laid on certain points—the very frequent change of position, and the massage, both long-continued, the prevention of over-distension of the bladder, and the avoidance of sedative drugs The cooperation of the patient and his untiring effort to recover is assumed, and this patient being a doctor was not required to report in the absence of symptoms Surely there must be a proportion of paraplegic patients who can be treated on similar simple lines? The emphatic verdict pronounced by Dr Riddoch suggests that he spoke from experience of similar cases

Bradford. PETER McEWAN

SUDDEN DEAFNESS

SIR,—Middle-ear and inner-ear factors associated with the sudden onset of deafness are recorded in your excellent leader of Feb 8 but you do not mention acute obstruction of the external auditory canal, presumably because this occurs so frequently In the experience of most practitioners this important cause is second only to otitis media in order of frequency In the presence of an accumulation of cerumen, for example, *sudden* deafness often follows the entry of water or other fluid into the canal (during ablution, swimming, instillation of aural drops, &c)

May I also comment on sudden deafness of unknown origin? Neurovascular dysfunction to the end-organ of hearing is postulated as a possible cause The late Mr Garnett Passe[1] found it possible to relieve the symptoms in Menière's disease by a procaine block of the cervical sympathetic chain, thereby producing vasodilatation This suggests that vasospasm is an important factor in some cases If vasospasm is also a cause of sudden deafness without vertigo, it would surely be right to treat such cases as an absolute *emergency* After a competent otological investigation, a therapeutic trial of a stellate block would yield useful information and if carried out early enough would have a greater chance of success Secondary thrombosis due to long-continued spastic occlusion would be less likely Compression of the nerve-fibres by œdema is another secondary factor of importance, for the degree of swelling and the length of time this lasts must influence the final prognosis

Rational treatment would therefore aim at the rapid relief of angiospasm, the prevention or limitation of thrombosis, and the alleviation of compression by a reduction of œdema The administration of nicotinic acid, as practised by Hallberg[2] and advocated in your leader, is too slow and too uncertain unless large doses are given intravenously Rapid vasodilatation can safely be brought about by a stellate block Thereafter *vasodilator* drugs could play an important role in the maintenance of an increased blood-supply There is no way of knowing whether or not thrombosis has taken place, and the anticoagulants would possibly be of help

Finally, adrenocorticosteroid therapy is known to aid the reduction of tissue œdema, and the anticongestive properties of cortisone or prednisone could well be employed

This new outlook requires a change of attitude from one of expectancy to one of action, and if the neurovascular theory is accepted much further research will be called for to determine the most promising line of treatment

London, W 1 F BOYES KORKIS

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[1] Acta oto-laryng, Stockh 1952 42, 133
[2] Hallberg O L Laryngoscope, 1956, 66, 1237

SIR,—Your leading article surveyed diverse causes and manifestations of sudden deafness We should like to add to your list by referring to a group of cases observed by us during 1956[1]

Our 11 patients were from 31 to 56 years of age and came from a rather limited geographical area The deafness, always one-sided, was of a sudden onset and was accompanied by tinnitus, sometimes also by vertigo After about three weeks 9 of the 11 patients were partially or entirely restored

The neurological and otological examination made us believe that the site of the lesion was neither the end-organ nor the acoustic nerve, but the region of the pontine cochlear nucleus The epidemic character and the simultaneous occurrence in this particular part of the country of similar affections of the brain-stem suggested an encephalitis

The neurological and otological examination made us believe that the site of the lesion was neither the end-organ nor the acoustic nerve, but the region of the pontine ochlear nucleus The epidemic character and the simultaneous occurrence in this particular part of the country of similar affections of the brain-stem suggested an encephalitis

Garnisonssjukhuset and Länslasarettet,
Sollefteå, Sweden

FOLKE MOLLER
CARL NENZELIUS

WHERE DOES MEDICINE FIT IN?

SIR,—It is probable that many readers will feel as grateful as I do for Dr Manning's most stimulating article[2] Particularly in the Western world "We have managed to change the pattern of disease that is all" As he remarks, "solving one problem leads to the appearance of new ones" It is very true that not only doctors, but most patients, apply "the standards and yardsticks of youth to the subject of time-induced deterioration" In youth we issue blank cheques in defiance of natural law and exploitation of reserves, these cheques are presented for payment in middle age Doctors could do much to help patients to understand their own difficulties and live patiently with what, so far at least, are unavoidable disabilities

In view of our limited knowledge of long-term effects, new drugs are often exhibited with almost maniacal recklessness In the Western world today mental stress is indeed a major factor in undermining physical health However, Dr Manning says "we have thrown religion overboard", and this is too sweeping Dogma and creed are failing to satisfy but the deep spiritual urge of man is seeking new expression and is commonly unsatisfied. Doctors do not usually help and have all too little time to consider what are regarded as "abstract things" Is it any wonder that a patient "will change from one doctor to another, seeking healing, but refusing to accept the fact that this must come from within himself" ? Do doctors help patients to understand this point or do they merely prescribe nostrums ? Dr Manning wishes that all doctors had some knowledge of geology and astronomy, but should we not add philosophy and comparative religion ? Reality does not consist only of things seen Allowing for a basic training, is it not possible that what we are is, over all, of far more importance than what we prescribe ? Man cannot live by bread alone This surely is really the main problem of the modern world

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[1] Acta otolaryng, Stockh 1957, 47, 158
[2] Manning R L Lancet, 1957, ii, 1274

Farnham Royal,
Bucks

M E M HERFORD

SIR,—I am sorry if I have aroused Mr Hewson's indignation (Feb 1), I am even sorrier that he has misunderstood me—perhaps I had better amplify my meaning I did not imply that there is no place for religion in man's outlook I merely stated that religion, as a guiding and comforting influence on mankind, is steadily and seemingly irreversibly declining

Furthermore, I would be the first to agree that a good priest or minister can do more good than a mediocre or simply an overworked doctor (but to be a good clergyman these days must be at least as difficult as to be a good doctor), and that medicine and religion can work side by side, as do, for instance, modern and traditional medicine in China (see Dr Fox's articles [1]) The trouble is that traditional (faith) therapy has been largely rejected by the patient in advanced communities, and people bring the problems that once were the burden and prerogative of the clergy to the doctor

Let me also assure Mr Hewson that there is not such a wide gap between the Christian doctrine, with which he identifies himself, and a cosmological point of view After all Christianity encourages surrender to a cause greater than the individual, and belief in the eventual eclipse of one's own troubles—after this life Whether you surrender your pride and presumption to faith or to reason is a matter of choice and background—but I suspect the results can be similar

Darwin, Australia

R L MANNING

SYRINGES CLEAN OR STERILE ?

SIR,—In the recent correspondence about the sterilisation of syringes, I was surprised to note that syringes of the cartridge type were not mentioned A leading manufacturer now offers a cartridge-syringe at a very modest price, and also a wide range of drugs in 2 ml cartridges adapted to permit an aspiration test I believe that there is no difference in cost between a conventional ampoule and a cartridge containing the same drug The widespread adoption of these cartridges would offer syringe services considerable relief

In my specialty of anæsthetics, however, the range of drugs so presented is not comprehensive enough to justify a change at present—the deficiency in the range applies, of course, to proprietary drugs manufactured by other firms I suppose that the same situation exists in other specialties

I write in the hope that some publicity for these observations may encourage the various interests involved to consider a business agreement, which would, in my view, bring benefits to all concerned

Carlisle

D HUNTER SMITH

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[1] *Lancet*, 1957, ii, 935, 995, 1053

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

SIR,—For his collation of the facts about pre-eclamptic toxæmia (Jan 18), all obstetricians are under a debt to Prof F J Browne, and it is with great respect that I differ from his thesis In brief, this thesis is that the placenta produces corticotrophin (A C T H), either directly or by stimulating the anterior pituitary gland, that the corticotrophin causes the adrenal cortex to produce excess of glucocorticoids and mineralocorticoids, that these substances—held responsible for pre-eclamptic toxæmia—are conveyed to the very structure that produced them (the placenta) and are destroyed by it when its oxygenation is normal, and finally that the placenta, even when ischæmic, can still encourage the production of these toxæmia-producing corticoids but has lost its capacity to destroy them The two last hypotheses appear to quarrel both with reason and teleology

In advancing this thesis Professor Browne makes comparisons which I believe to be inapplicable

(*a*) Deoxycortone influences are invoked This substance does not, so far as is known, occur naturally despite assiduous search it has never been identified physiologically Its property of equal potency in retaining salt and provoking hypertension is not shared by any other corticoid, in all of which one or other function predominates

(*b*) In the case described by Altschule and Zamcheck,[1] a change was indicated by the severe hypoalbuminæmia (4 4 mg per 100 ml) and concomitant albuminuria This excludes it from comparison with pre-eclamptic toxæmia in which there may be considerable œdema without any preceding or accompanying albuminuria and in which hypoalbuminæmia of such extent does not occur [2]

(*c*) Nor can increased vascular permeability, indicating a toxin's influence, be advanced as an explanation of pre-eclamptic toxæmia, for Switzer [3] showed that in 20 toxæmic women the protein content of œdema fluid (when uncontaminated with capillary fluid) averaged 0 23% per 100 ml , which means that it cannot have escaped through the capillary wall

(*d*) The suggested resemblance of normal pregnancy to Cushing's syndrome is not valid The plethora, hirsuties, moon-face, buffalo obesity, wasted limbs, sex-gland atrophy, polycythæmia, wide purple striæ, alkalosis, and above all the *hypokalæmia* (responsible for asthenia and muscular weakness) met with in Cushing's syndrome or in overdosage of cortisone (the hormone held responsible for the syndrome) present a vastly different picture from normal pregnancy or pre-eclamptic toxæmia

The dissimilarity of the latter is further emphasised by the fact that in Cushing's syndrome retention of sodium and water, is effected by the tubule whereas there is clear evidence that in pre-eclamptic toxæmia it is effected to a considerable extent by the glomeruli Page [4] has demonstrated in toxæmia a 60% reduction in glomerular filtration-rate, and renal biopsies provide unquestionable evidence of an underlying cortical renal ischæmia responsible for this reduction [5]

Nor is the hypertensive mechanism provoked by corticoids comparable to that met with in pre-eclamptic toxæmia Shorr [6] has shown that vasoexcitor substance (V E M) is never to be found in the renal-vein blood of animals with hypertension induced by corticoids, yet it is present in renal-vein blood in experimental renal hypertension [6] and clinically in essential hypertension [6] and in toxæmia [7]

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1 Altschule, M D , Zamcheck, N *J clin Endocrin* 1942, 2, 269
2 Mack, M C Plasma Proteins in Pregnancy Oxford, 1955
3 Switzer, P K , Hester, L L , Mulam, J W , Ownby, F D *Amer J Obstet Gynec* 1950, 60, 427
4 Page, E W *West J Surg* 1957, 65, 3
5 Pollak, V E , Pirani C L , Kark, R M , Muehrcke, R C , Freda, V C , Nettles, J B *Lancet*, 1956, ii, 59
6 Shorr, E , Zweifach, B M Proceedings of First Clinical ACTH Conference 1950 London P 294
7 Dexter, L , Haynes, F W , Siebel, R E *Amer J Physiol* 1944, 150

Further evidence against the suggested relation of pre-eclamptic toxæmia to Cushing's syndrome is the fact that in pre-eclamptic toxæmia the level of corticosteroid excretion cannot be correlated with the level of the blood-pressure,[8] while Venning [9] has shown that the amount of the urinary secretion of the formaldehydogenic corticoids in these cases may be no higher than it is in normal pregnancy

The conditions again are sharply differentiated by the effects of treatment Rest and salt restriction have unique therapeutic value in pre-eclamptic toxæmia This certainly is not so in Cushing's syndrome, where, according to Knowlton,[10] salt restriction exacerbates the hypertension induced by cortisone The two conditions are further separated by the presence, in pre-eclamptic toxæmia, of casts and red blood-cells in the urine, and by the possible supervention of fits Most important of all is the fact that the alleged responsible hormone, cortisone, when injected into the toxæmic patient, does not exacerbate the toxæmia (Margulis [8])

The possible responsibility of aldosterone for pre-eclamptic toxæmia is also advanced, but both Venning [11] and Rinsler [12] have found that the secretion of aldosterone is much diminished in the later stages of active toxæmia Similarly, excess of antidiuretic hormone cannot play any substantial part in the ætiology, for Dieckmann [13] says that patients with diabetes insipidus, entirely lacking this hormone, have on several occasions developed pre-eclampsia

Some of the data proffered by Professor Browne are, I believe, misinterpreted and therefore misapplied

(1) The significance of intracapillary glomerular sclerosis in diabetes is overlooked It should be realised, first, that occult renal changes—facilitating the uterorenal reflex—can be responsible for hypertension,[14] and secondly that incipient hypertension predisposes to toxæmia These facts suffice to explain the higher incidence of pre-eclamptic toxæmia in diabetic women there is no need to invoke corticoids

(2) The hormonal influence of hydatidiform mole cannot be an ætiological factor, since toxæmia is absent in cases of chorionepithelioma where chorionic gonadotrophins are equally overproduced (Acosta-Sison [15] has recently shown that the height of the fundus is related to the height of the blood-pressure—evidence of heightened uterine tone that supports the role of the uterorenal reflex [16])

(3) The very content of Byrom's [17] invaluable experiment is the renal ischæmia on which it is based He clearly demonstrated that all the vasospasm effects were entirely due to the clamping of the renal artery removal of the clamp abolished the vascular manifestations including the encephalopathy Here again is proof of the renal ischæmic change which I regard as a result of the uterorenal reflex [4] The postpartum rise in blood-pressure can be correlated with the tonicity of the uterus and its occurrence therefore supports my view that the uterorenal reflex causes the "toxæmia" (see below) A corticoid explanation for this postpartum hypertension is not in keeping with the facts, since it is well known that considerable diuresis follows delivery If the hypertension were the result of corticoid influence and not of renal ischæmia, salt and water retention rather than diuresis should accompany the rise of blood-pressure, for the predominant effect of corticoids appears to be on salt and water rather than on blood-pressure Severe renal ischæmia (e g, by Goldblatt clamping), on the other hand, primarily provokes hypertension (The degree, the extent, the speed of onset, the duration, the existing hydration, and the accompanying vasospastic state all contribute to vary the effect of cortical renal ischæmia on the sequence and the extent of the œdema, the hypertension, the fits, the albuminuria, and the anuria)

Professor Browne enunciates two hypotheses which I regard as unnecessary

The first concerns protective influence of the placenta against corticoid effects Here again one pharmacological action is singled out for consideration, and the claim is made that the hypertensive effect is neutralised by the non-ischæmic placenta of normal pregnancy But the paradoxical or reversal action that reveals itself on cortical overdosage is overlooked Prunty [18] has shown that, though cortisone or hydrocortisone originally cause active retention of water and salt, this is reversed on continued administration The same is true of corticotrophin [18] Sayers,[19] Sprague,[20] Ingles,[21] and many others have recorded similar reversal findings either with synthetic or with naturally occurring corticoids, which in general tend to restore normal levels of water and salt in the tissues and to support the normality of tissue and organ responses to stimuli arising from the non-adrenal systems This occult action helps to explain their presence in greater amounts both in normal and in abnormal pregnancy, without obvious pharmacological effect Especially is it to be remembered that they can control water and electrolyte movements from intracellular to extracellular space and vice versa—movements difficult to uncover yet revealing themselves in otherwise inexplicable pre-eclamptic phenomena such as sudden œdema

The second unnecessary hypothesis is that corticoids have the power of vascular sensitisation This explanation is not needed and can in fact be denied Vascular sensitisation results from renal ischæmia, as is revealed by the fact that renoprival hypertension ensues far more rapidly when the kidneys have been subjected to clamping before their removal, indicating that the ischæmic kidney has prepared the hypersensitive soil (Ledingham) [22] Equally important is the denial of corticoid sensitisation by the experiments of Schorr,[23] who demonstrated that in animals made hypersensitive with deoxycortone the mesenteric vessels were not more responsive to adrenaline Perera [24] actually found a decline in arterial tension in hypertensives after long-continued dosage with cortisone—an effect that led him to conclude that cortisone has "no humoral action directly"

Professor Browne's difficulty in accepting the uterorenal reflex as responsible for postpartum eclampsia will be removed if the following facts are appreciated

(1) Cortical renal ischæmia has been seen to occur postpartum in the experimental animal and to coincide with the postpartum uterine contractions (Franklin [25]) as plainly as they do with the contractions consequent on uterine distension or the contractions of labour Further proof of the increased tone of the myometrium postpartum, on which the uterorenal reflex is indirectly based, is provided by Schofield [26] who finds that the concentration of contractile proteins in the myometrium is directly proportional to the œstrogen present, and that there is a postpartum rise in adenosine triphosphate (which heightens tension) lasting for at least three days These two facts help to explain the occurrence of postpartum eclampsia through the operation of the uterorenal reflex

Professor Browne's own thesis cannot explain the recrudescence of toxæmia at labour, after its abatement days earlier on the death of the retained fœtus Fœtal death connotes placental death, and consequent cessation of the placenta's alleged eclamptogenic corticotrophin effects, at most within three days—the time-limit set on their activity by Professor Browne himself when explaining by his thesis the longest possible delay in the onset of eclampsia postpartum When labour is delayed beyond this time, the postpartum rise of corticoids observed by Gemzell[27] must therefore fall on presumably "normal soil" If it fails to provoke eclampsia in the like soil of normal pregnancy, it must fail to do so in these circumstances too

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[8] Margulis R R, Hodgkinson C P, Ratan W C, Jewell J S *Amer J Obstet Gynec* 1954 67 1257
[9] Venning E H, Sweet B Simpson G A *ibid* p 542.
[10] Knowlton A I Loeb E N Stoerk H C, White J P Heffernan, J F *J exp Med* 1952 96 187
[11] Venning E H Primrose T, Caligaris L C S Dyrenfurth I *J clin Endocr* 1957, 17 473
[12] Rinsler M G Rigby B *Brit med J* 1957 ii 966
[13] Dieckmann W J Toxemias of Pregnancy 1953 S Louis
[14] Wilson C, Ledingham J M Cohen M *Lancet* Jan 4 1958 p 9
[15] Acosta-Sison H *Amer J Obstet Gynec* 1956 71, 1279
[16] Reynolds S R M Baker J T *Contr Embryol Carneg Instn* 1951, 34 75
[17] Byrom F B *Lancet* 1954 ii 201

[18] Prunty F T G *Brit med J* 1953 i 852.
[19] Sayers G *Physiol Rev* 1950 30 241
[20] Sprague R G *Amer J Med* 1951 10 567
[21] Ingles D J R *Endocrinology* 1946, 39 52
[22] Ledingham J M *Brit med Bull* 13 33
[23] Shorr, E. Proceedings First Clinical ACTH Conference, p 314 London, 1950
[24] Perera, G *ibid* p 285
[25] Franklin K J *Lancet* 1953 ii 1141
[26] Schofield B *J Physiol* 1957, 138, 91

Finally, judging by Gaunt's[28] experiments, the corticoids seem to be needed in rats to allow renin (which induces renal cortical spasm) to provoke a state identical with eclampsia But the ætiological emphasis is entirely on renin, for the eclamptic state disappears on its withdrawal—this effect being hastened by administration of hydrallazine to reduce renal resistance

Renal resistance (cortical renal vasospasm) is a product of the uterorenal reflex that is invariably elicited when the myometrium is resisting stretch[29]

Professor Lennon (Feb 15) holds that noradrenaline is the pressor factor in toxæmia, entirely accounting for the generalised vascular spasm and thereby for the many pathological changes Presumably he has arrived at this conclusion from his success in neutralising this humoral substance

Certain misgivings immediately arise

Toxæmia can occur in non-hypertensive patients, as Professor Lennon admits In fact it is a common experience that it usually does so arise, for the œdema of its earlier stages is unaccompanied by hypertension and therefore *without* noradrenaline intrusion Neither is noradrenaline capable of causing water and salt retention (present throughout pre-eclampsia) experimentally or clinically in phæochromocytoma

By regarding placental ischæmia as the *basic* pathological feature of pre-eclampsia he is overlooking the fact that since noradrenaline has never been demonstrated in the placenta (it lacks nerve-fibres) this feature can have no *basic* relevance to his thesis Defective transmethylation of noradrenaline to adrenaline has never been definitely shown to be a cause of hypertension[30] Yet Professor Lennon claims that it can be overcome by dieting He has been impressed by the effectiveness of diet in checking the toxæmic process, but overlooks the fact that the regimen is in the first place directed against the increase of the œdema—a disturbance of salt and water metabolism that noradrenaline cannot remotely affect Again, effective transmethylation, by converting excess noradrenaline into excess adrenaline, should thereby produce dramatic pharmacological effects, and these the successfully dieted toxæmic patient does not exhibit

Obstetricians everywhere must inquire more deeply

London, W 1 — JOHN SOPHIAN

RUPTURE OF SPLEEN WITH DELAYED SYMPTOMS

SIR,—The case reported below showed several points of clinical interest, and I record it here because this abdominal emergency should be kept in mind

A woman, aged 24, was admitted shocked She had been perfectly well until two days before admission, when persistent epigastric pain began On the day of admission she vomited twice and fainted

She was pale, with a thready pulse (120), no pyrexia, blood-pressure 90/70 mm Hg Cardiovascular system normal Bruise 3 in in diameter on outer aspect of the left arm, none elsewhere Abdomen slight discomfort all over with guarding 2 in below the xiphoid process No bowel sounds heard and no free fluid Breathing was shallow, and, at the end of inspiration, pain in the abdomen was worse She admitted that week previously she had slipped on a mat in the house, an when the point was put to her she admitted that she ha bumped her left ribs as well as her left arm After resuscitatio with plasma (B P 115/70) further examination indicated obviou free fluid

At laparotomy, blood was found in the peritoneal cavi (1–$1^{1}/_{4}$ pints) A tear 2 in long was felt on the posterior aspe of the upper pole of the spleen, which was mobilised with ea and removed As the spleen was being severed, two splen unculi were noticed, each 1 in in diameter, one abov the splenic vessels and the other "sitting" above th splenic flexure of the colon Postoperative course wa uneventful

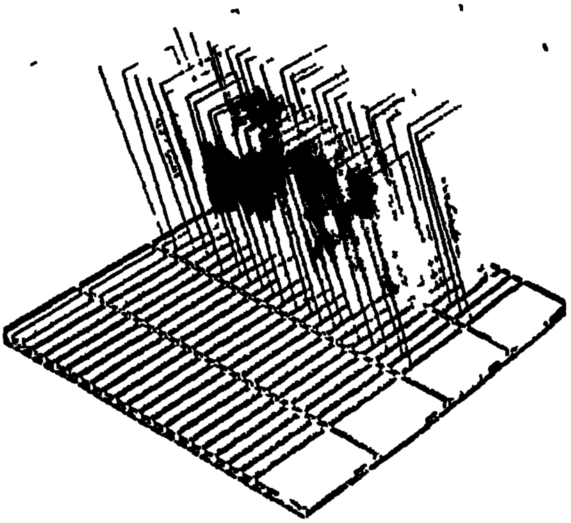
This was a traumatic rupture of the spleen a wee before admission, either subcapsular or sealed off wit clot. There were leaks two days before admission and o the day of admission, the last one ceased with the dro in blood-pressure, only to begin again after resuscitation

Weymouth and District Hospital — JOHN M E JEWERS

A SLIDE-DRYER SLAB

SIR,—The slide-dryer slab illustrated here has prove useful

It consists of a flat piece of 'Perspex' $^{1}/_{4}$ in thick and 6 in square It is scored by 20 lines, and by a further 3 at right angle to these This allows 80 slides to be stacked on it The averag microscope slide will stay in it at a slightly slanting angle The front part of the slab is not scored, so that it is easier to carry it



The slide-dryer has been adapted after many modifications from a wooden model which I noticed in the laboratory of the Centre Régional de *Transfusion Sanguine* at the Hôpital St Antoine in Paris, during the tenure of a Ciba Foundation Anglo-French exchange bursary The choice of wood seemed unfortunate, because it warps even when xylol is used *This is* avoided by the use of a plastic material

The slide-dryer is particularly useful for blood slides *which*, after examination with the oil-immersion lens, have been in xylol and which are to be dried for filing away *It is* also useful for large-scale mounting of histological slides for class purposes The excess water drains away satisfactorily A half model has also been prepared, which is useful in smaller laboratories

The dryer has been made to my specification by the Visijar Laboratory Supply Co Ltd, 149, London Road, Croydon, Surrey

St Mary's Hospital Medical School,
London, W 2 — E NEUMARK

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27 Gemzell C A *J clin Endocrin* 1953 13, 898
28 Gaunt R Renzi, A A *Ciba clin Symp* 1954, 6, 30
29 Sophian, J *Excerpta med Amst* 1958, section x, vol 2, p 1
30 Goldenberg M Pines K L, Baldwin, E de F, Greene, D H, Roh, C E *Amer J Med* 1948, 5, 792

A FUNCTIONAL NECESSITY

SIR,—Your leader[1] has aroused a great deal of comment, mostly adverse. In your penultimate paragraph you refer to the S.H.M.O.s as an incompatible group, but surely you did not mean to imply that S.H.M.O.s have only mediocre attainments. It does not seem to be generally appreciated what a wide range of ability is included in this grade. At one end of the scale there are those who rely on experience only (from which they may or may not have gained) but at the other end are those who are better qualified and more experienced than many of their consultant colleagues. Perhaps because of this wide range of ability little has been done to rectify the just complaints of S.H.M.O.s in spite of the large volume of correspondence about the position.

At present the Whitley Council is considering the cases of many hundreds of S.H.M.O.s who claim they are doing consultant work, and it seems that as a result a few more consultant posts will be created. However, there is a strong feeling that this upgrading will depend more on the proximity of a consultant than on ability. It seems that, in the chest services at least, recommendations were made some two years ago as to the appropriate S.H.M.O.s to upgrade, and the present machinery is intended to give an air of respectability to something already decided. It is noteworthy that a resolution of the B.M.A. tuberculosis and diseases of the chest committee in 1955 made no mention of ability or qualifications with regard to those to be upgraded.

Your suggestion that the S.H.M.O. grade should be perpetuated in any form will meet with little support from those who have experienced the ignominy of this grade. It is alleged that the S.H.M.O. is under the general supervision of a consultant, but no-one has yet been able to define what this means, and yet you suggest this state of affairs should continue. Supervision in a teaching hospital is one thing, but supervision at the periphery by a consultant who is younger, less knowledgeable, and less well-qualified is completely different. Supervision under such circumstances is not only embarrassing to both but can have unpleasant repercussions. It must also be realised that some full-time consultants lose their zest for work once appointed, and the S.H.M.O. bears the brunt of the work for which he receives little thanks and no financial reward. In the event of a difference of opinion between consultant and S.H.M.O. the various committees appointed to investigate must invariably support the consultant as the senior officer, however wrong he may be. Of course this can and does lead not only to a sense of frustration but eventually to a lowering of standards, and this must be avoided at all costs.

Surely an answer to this complex problem would be to create enough senior posts with an adequate salary graded according to the responsibility and the work involved. Naturally a consultant in a teaching centre would command a bigger salary than one at the periphery, but that is how it should be. Such a step would automatically do away with the iniquitous system of merit awards. It would also ensure some circulation of appointments. A consultant in a south-coast resort would not think of moving to the industrial areas at present, but if a higher salary were offered might well be tempted, thus leaving his post open to fair competition. A method should also be found whereby an appointment is made solely on ability and not, as at present, by the hierarchy who wish to place their own candidates.

Finally I should like to re-echo Mr Berrill's point in his letter of Dec. 14. Something must be done, and done soon, and something more than the present Whitley Council procedure, which may well prove to cause more resentment than exists now. Whatever is done should see the end of this S.H.M.O. grade, and not its re-emergence under another name.

Bournemouth O. D. BERESFORD.

*** Like Dr Beresford, we do not want to see the S.H.M.O. grade perpetuated. We propose that it should be replaced by the new grade of "specialist" which would differ from it in two important ways: (1) it would be the grade through which all future consultants must pass, and (2) it would have a salary range overlapping, at the top, that of consultant. Dr Beresford, as we understand him, would prefer to reduce the status of consultant by giving it to all present S.H.M.O.s but would reward merit by paying higher salaries for work at teaching hospitals or in unpopular areas. He seems to us to underrate the advantages of the present system by which equal basic salary scales have attracted consultants to the periphery and by which a man can get personal recognition for good work wherever it is done—without moving to some other post officially scheduled as more important.—ED. L.

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[1] *Lancet*, 1957, ii, 1099.

Parliament

Help for the Family

IN an adjournment debate on Feb. 12 Mr ANTHONY KERSHAW suggested that there was a tendency today to forget the role which the family still played in the care of old people. In a recent small survey in Bethnal Green it was found that about half the old people were looked after by their families. But if old people were to be kept at home, we must, he said, extend the domiciliary services and give the family more help. Not only should there be a system of regular visits to old people living alone, but also to families looking after old people. The strain could be heavy and was often discovered too late, when a daughter or a niece collapsed and she and her aged charge had both to be moved to hospital. Something should be done in advance to help families. The older members could, for instance, spend short visits in institutions to give the younger member a rest. Again would the Minister and his colleagues consider the possibility of a constant attendance allowance, such as was paid for war pensioners, for families looking after bedfast relations? He believed that timely help to the family might save the community great expense.

Mr RICHARD THOMPSON, parliamentary secretary to the Ministry of Health, agreed that old people should be looked after as long as possible in their own family and in their own home. Reviewing the health and welfare services which are available in the home, he said that the local authorities' health visitors in 1956 paid about 1 million visits to the aged and chronic sick, and the home nurses paid about half of their 25 million visits to patients over sixty-five. This last figure showed the growing need of old people, for three years earlier only a third of the nurses' visits were made to the aged. The number of home helps had risen from 11,000 in 1948 to 39,000 in 1956, and in that year 68% of the applications for help came from households with an aged or chronic invalid. Other ways in which old people were helped in their own homes, often by voluntary organisations, were the night attendance and evening service, the laundry service, the chiropody service, and meals on wheels.

He could not discuss in an adjournment debate the suggestion put forward for a constant attendance allowance, for that would require legislation.

Notification of Acute Rheumatism

On Feb 17 Dr Edith Summerskill prayed against the Acute Rheumatism (Amendment) Regulations, 1956, asking why notification of this disease should be restricted to certain parts of England Cornwall, Lindsey in Lincolnshire, Bristol, Grimsby, Hull, Lincoln, Salford, Sheffield, and Ilford were in her view an extraordinary collection of places which were not necessarily representative of England She believed that they had been chosen in 1947 when notification was started, because it was believed that these areas had specialists capable of handling the chronic rheumatic condition which followed acute rheumatism But in the last ten years the National Health Service had tried to allocate specialists more uniformly over the country and she wondered whether it was still necessary to limit notification In particular she would like to see more of the damp Northern cities and more of the poorer parts selected

Mr Richard Thompson, parliamentary secretary to the Ministry of Health, said that notification had been introduced in selected areas, on the recommendation of the rheumatic fever committee of the Royal College of Physicians of London, to provide an index of the prevalence of the disease in the country as a whole and to facilitate the continued supervision of children who had had the disease The areas had originally been chosen because of the known existence in them of competent observers who could assess the value of the supervisory procedures used But this did not mean that the same methods of treatment were not available in other areas Originally 5 areas had been chosen Since then 4 further areas had been selected and he did not rule out the possibility of further additions But extension to the whole country would not be justified at least for the present as this was not necessary to provide the necessary statistical information It must be realised that notification in this instance was more of a research observation exercise than a treatment exercise

QUESTION TIME

Possible Protection Against Radiation

Sir Wavell Wakefield asked the Minister of Health, as representing the Lord President of the Council, in view of the progress in the United States of America with research into the possibility of production of a drug to counteract poisoning or death by radiation in the event of a nuclear war or accident, what advance had been made in the United Kingdom in this direction —Mr Derek Walker-Smith replied The Medical Research Council has for some ten years actively supported work on substances that might protect against the effect of ionising radiations Substantial progress has been made experimentally but the results are not yet applicable to the treatment of human beings

Psychiatric Treatment of Criminals and Delinquents

The World Health Organisation has allocated to the United Kingdom four places on the seminar on this subject which is to be held at Copenhagen, and the Minister of Health has appointed Dr W F Roper, principal medical officer, H M prison, Wakefield, Dr R C Simpson, consultant psychiatrist, and Mr Morrison, principal psychologist, H M prison, Wormwood Scrubs, and Dr Inch, medical adviser to the Scottish Prison and Borstal Service

Merit Awards

The total number of merit awards in England and Wales at Dec 31, 1957, was 2343 The total annual cost was about £2 million, which is equivalent to about a quarter of the estimated total of the recipients' salaries, including the awards

Cruelty to Animals

The five inspectors under the Cruelty to Animals Act, 1876, are all medically qualified They are Dr P L C Carrier (chief inspector), Dr F Elliott, Dr E H Hall, Group-Captain G Struan Marshall, and Dr B Walker

Obituary

ERNEST JONES

M D Lond, Hon D Sc Wales, F R C P, D P H

Ernest Jones, who died on Feb 11 at the age of 79, was honorary president of the International Psychoanalytical Association, and the most eminent psychoanalyst since the death of Freud, whose biography he wrote

Born and brought up in Wales, he attached some importance to his origins, since he held that the Welsh, like the Jews, were a religiously minded people whose outlook was coloured by their history of defeat and suffering From University College, Cardiff, he came to London and studied at University College Hospital His interests were wide, but neurology had a particular attraction for him

Jane Bown

He was house-surgeon to Victor Horsley, attended the National Hospital, Queen Square, as a clinical assistant, and published several neurological papers, chiefly concerned with allochiria and other disorders of sensation Among his contemporaries and friends at U C H were Bernard Hart and Wilfred Trotter, then and always much interested in psychological matters Jones experimented with hypnosis and frequented mental hospitals, especially Long Grove (where Dr Hart then was), Bethlem (to see his friend W H B Stoddart), and Claybury (where Frederick Mott had his laboratory)

In 1905 Freud published in German a fragment of an analysis, revealing the dramatic story that lay behind a young woman's hysterical symptoms This came to Jones' knowledge, probably through a notice by Havelock Ellis It accorded with a view well expressed in Wilfred Trotter's remark to Jones, apropos of hysterical convulsions "One sees only the blood trickling under the door, but we know nothing of what tragedy is being enacted inside" Jones set to work to learn German so that he could acquaint himself with Freud's writings, which promised to explain much that he had found lacking in the brilliant and detailed French literature on hysteria He acquainted himself with the main ideas, though he did not read Freud's *Interpretation of Dreams* until a year or two later However, in 1905 he undertook the psychoanalysis of a patient —the wife of an American neurologist it was the first analysis to be conducted outside the German-speaking countries Jones presently met Jung and they arranged an international psychoanalytical congress which was duly held at Salzburg in 1908 Jones and Trotter were the British members Here he met Freud for the first time, and read a paper on Rationalisation From then on his professional and personal life was intimately linked with the furtherance of psychoanalysis He continued for a time, however, to extend his psychiatric knowledge by visits to Paris and to Kræpelin's clinic and institute in Munich

At the instance of Osler, Jones was invited in 1909 to take charge of the new psychiatric clinic in Toronto Here, however, as previously in London, his psychoanalytical work brought him into undeserved odium, and in 1911 he decided to return to England The years in North America had been spent in tireless activities for the spread of psychoanalysis by teaching, lecturing, organising meetings, and founding the American Psychoanalytic Association A review of developments in psychopathology written by Jones at that time, and published by Mott in the L C C Archives of Neurology and Psychiatry in 1911, contained the characteristically shrewd observation that in England "the subject is viewed with a cold antipathy

In America, on the other hand, there is a widespread cordiality, though the value of this is largely counterbalanced by the superficial and uncritical views that, except in a comparatively small circle, generally prevail Readiness to accept a psychogenetic origin of certain maladies is much more widespread in the American medical profession than in the English and there is also in that country a very general interest taken in the problems by the laity "

Ernest Jones was a loyal friend and devoted adherent of Freud Early in their association he proposed that a small group of trustworthy analysts should form a secret council to advance and defend the cause of psychoanalysis, and in 1913 this committee of intimates assembled, with Jones as founder-chairman In this and many other ways he lightened the burden which rested on Freud His good sense, judgment, and diplomatic skill were qualities of the utmost value to psychoanalysis during the turbulent years of dissension within and antagonism from without Freud fully recognised this (apart from a passing shadow in 1922) and knew he could depend on Jones' integrity and support When the Nazis marched into Vienna, Jones took prompt and courageous steps to rescue Freud and his family from the danger and humiliations they were exposed to in Vienna

The introduction and furtherance of psychoanalysis in England was Ernest Jones' especial mission He worked without regard for personal convenience or advantage to bring this about, though his health was for a long period troubled by an undiagnosed metabolic disorder He travelled widely and attended innumerable congresses, but he gave the bulk of his time, apart from his practice, to fathering the British Psycho-analytical Society, the *International Journal of Psychoanalysis* (which he founded and edited from 1920 to 1939), the International Psychoanalytical Library (familiar green volumes which issued steadily from the Hogarth Press), and other activities centred on London and usually on Jones himself The institute which was set up in 1924 for training psychoanalysts owed a great deal to him although a few months' intensive analysis by Ferenczi in 1913 was all the training he himself had had, he recognised that something more systematic and thorough was required for the succeeding generation Another service to psychoanalysis in this country, on which he himself set much store, was winning from a special committee of the British Medical Association in 1929 a favourable report he called it "my most difficult achievement on behalf of psychoanalysis "

Jones wrote fluently and clearly His output of psychoanalytic articles was large, and ranged from technical case-reports and theoretical expositions to applications of psychoanalysis to anthropology, literature (here his study of Hamlet was notable), religion, politics—and even chess-playing, to which he was much addicted He wrote a parergon in 1931—a manual on the elements of figure-skating, of which a revised edition was called for in 1952 it is a model of straightforward simple instruction. His outstanding literary work was his biography of Freud written with intimate knowledge, immense respect this side idolatry, and scrupulous regard for detail, it deserved the acclaim which greeted it as a moving and faithful picture of a man of genius, drawn by a gifted disciple

Ernest Jones had, and recognised in himself, obsessive tendencies which enabled him to organise his knowledge and deal thoroughly with masses of detail, with this went in his earlier years a tendency to be rather critical of others As time passed, however, he became tolerant, and this was strikingly illustrated in his support of Mrs Melanie Klein when she put forward controversial views that diverged from those of Freud and most other psychoanalysts of the time In the valedictory address he delivered to the British Psychoanalytical Society when he was presented with his portrait, he concluded by advocating greater tolerance towards diversities "or even divergencies' this was the attitude he consistently displayed during the latter part of his life

He was married in 1919 to Katherine Jokl of Vienna she and his daughter and two sons survive him

GEORGE CARSON SWANSON

M.B Glasg

Mr George Swanson, consulting surgeon to Glasgow Royal Infirmary, died on Feb 7 at his home at Balfron at the age of 69

He qualified first as an engineer, but after seven years' work and travel, he turned to medicine—his father's profession After graduating M.B from the University of Glasgow in 1916, he spent some time at University College, London, and took the English conjoint qualification His first staff appointment was in 1919, as junior assistant to Prof Robert Kennedy at the Royal Infirmary, and his colleagues regarded it as a tribute to his tact, good humour, and Highland dourness that he got along with the choleric and eccentric "Rab" for five years His rise was steady and his work was ever more widely appreciated He was appointed surgeon in 1935

J A. G B writes

Swanson was a sound and safe general surgeon with a particular flair for anything mechanical He possessed a complete little engineering workshop where he modified or evolved surgical instruments Many of these went far afield as prototypes

He was shy in the company of strangers, but entertaining and happy with his friends He was averse to publication or public lecturing, but he was a first-class and impressive teacher A few years before he retired in 1953 he acquired a farm and spent many happy days manipulating a favourite tractor

Mr Swanson leaves a widow and a daughter

FREDERICK JAMES RUSSELL STONEHAM

M R.C S , F F.A. R.C.S , D.A.

Dr F J R Stoneham, consultant anæsthetist in the Windsor group of hospitals, died at the Canadian Red Cross Memorial Hospital, Taplow, on Jan. 14 at the age of 48

He was born at Weymouth and was educated at Harrow and at Guy's Hospital, qualifying in 1937 He held house posts at Guy's before becoming anæsthetic registrar In 1941 he joined the Royal Air Force and served, with the rank of squadron-leader, as an anæsthetist until he was demobilised in 1945 He was than appointed senior anæsthetist to the Birmingham Accident Hospital, where he was in charge of the shock and resuscitation unit

In 1948 he moved to Windsor and was appointed anæsthetist in the Windsor group of hospitals, and in 1950 he was graded consultant anæsthetist His main work was carried out at Maidenhead Hospital, Heatherwood Orthopædic Hospital, Ascot, and the Canadian Red Cross Memorial Hospital, Taplow

He was one of the Windsor team which investigated the use of 'Plasmosan' in the treatment of shock. In 1956 he was elected F.F.A R.C S

A colleague writes

Stoneham was particularly interested in anæsthesia for children, with whom he was most understanding and quickly gained their confidence, while his attention to detail and his obvious enthusiasm for his work gained for him the respect of his colleagues

To his work he gave much thought and care, constantly striving to improve the standard of anæsthesia He gave to his patients the same kindness and consideration which made him so many friends He was devoted to his family and his home.

Dr Stoneham leaves a widow and two daughters

Notes and News

A HEALTH-EDUCATION JOURNAL

THE International Union for Health Education of the Public has begun to issue a periodical, the *International Journal of Health Education* In the first issue welcoming messages from Prof Jacques Parisot, president of the Union, and Dr M G Candau, director-general of the World Health Organisation, are followed by an article by Dr John Burton entitled Doctor Means Teacher The journal, whose content is largely non-technical, is to be issued quarterly in French and English editions The subscription is 12 Swiss francs a year, further information may be obtained from the editor at 3, rue Viollier, Geneva, Switzerland

THE WELFARE OF SPASTICS

ON Jan 11 a joint meeting was held of the medical advisory committees of the British Council for the Welfare of Spastics and the National Spastics Society Prof Alan Moncrieff was in the chair, and the following subjects were discussed nomenclature and classification of cerebral palsy, facilities for early diagnosis of cerebral palsy in children under school age, and management and training of these children It was agreed that a further joint meeting of the full medical committees should be held in six months, and it is hoped that these meetings will be held regularly twice a year This is a first step towards closer integration [1] of the professional and technical work of the two societies

REGIONAL MEDICINE IN PUERTO RICO

TO its strategic Operations Bootstrap, Commonwealth, and Serenity,[2] Puerto Rico is now adding the tactical Operation Regionalisation [3] This West Indian island, which has a population of $2^1/_4$ million, was ceded by Spain to the United States in 1899, by the constitution of 1952, the Commonwealth of Puerto Rico is self-governing in internal affairs

At present the health, medical, and welfare services are administered centrally the division of hospitals administers the five district hospitals, the division of public health, through the municipalities, administers the health centres (each of which houses a health unit, municipal hospital, and welfare unit), and the division of public welfare administers five welfare districts The services are now to be decentralised the country will be divided into five districts Each will have several community health and welfare centres linked operationally with a district hospital, " to produce the effect that the area is served by one giant hospital with branches geographically distant but functionally as closely related as if they were the wards or divisions of a large medical centre " The doctors in the health centres will be on the staff of the district hospital To the hospital will be referred patients for special diagnosis or treatment (including major surgery) and women having a first or a complicated labour The health centres will have provision for routine laboratory tests and fluoroscopy, and will cooperate where necessary with tuberculosis, chronic-disease, and mental hospitals The five district hospitals will be linked with the much expanded metropolitan medical centre, which comprises a medical school and several hospitals

Four chief benefits are claimed for regionalisation The quality of service would benefit by diffusion of the highest standards from the teaching centre to the periphery Regional administration would be more economical Preventive and curative services would be available equally to those in town and country Local citizens would be encouraged to " improve the community's health through their own efforts "—an important point, for " the cost of tax-supported health care has probably reached the upper limit which the existing system of taxation can support ", while expenditure on building and on improving doctors' conditions will have to be increased It is hoped that medical insurance schemes will be widely extended

Eighteen months ago work was begun on the organisation of a pilot-plant scheme for the Bayamón area, one of the five regions It is expected that the " experimental research action phase " there will take five years, the experience gained will be used in organising the other four regions

A PORTABLE ELECTROENCEPHALOGRAPH

ELECTROENCEPHALOGRAPHY has always been associated with complex, bulky, and expensive apparatus, with an insatiable appetite for paper A new instrument, described by McDermott,[1] shows what can be achieved by an unconventional approach to the various technical problems which arise in designing a compact electroencephalograph

This instrument does not produce a written record, but displays up to six traces simultaneously on a cathode-ray tube with a long-persistence screen This is done by the use of a pulse time multiplex system—a method more familiar to the telecommunications engineer than to the electrophysiologist, for it is one of the possible ways of transmitting a number of messages over a single channel The display is identical in appearance with that of a normal E E G record, since the time base can be adjusted to run at the standard speeds of 1, 3, or 10 centimetres per second An obvious disadvantage is that the record is visible for only a few seconds at a given time, but, provided the operator knows what to watch for, it is adequate for selecting patients for more detailed investigations with a normal electroencephalograph The location of foci by the method of " phase reversal " was at first thought to need special circuit arrangements, but, in practice, phase reversals—at least in adjacent traces—proved reasonably easy to detect No form of time marker is fitted, but an experienced operator can estimate frequencies between 1 and 15 cycles per second to an accuracy of about 1 cycle per second

The electroencephalograph is mains-driven, and, complete with its power supply, weighs just over 40 lb The weight of stabilised power pack can be considerably reduced, in McDermott's opinion, by replacing certain of the thermionic valves in the instrument by transistors By the use of an electromagnetically focused radar P P I (plan position indicator) tube, a recorder which writes on ' Teledeltos ' paper has been developed, and shows considerable promise

PAY IN THE SERVICES

INCREASED rates of pay and allowances in each of the three Services for regulars of all ranks based on the United Kingdom are to be introduced on April 5 [2] The new basic rates for non-specialist medical officers are as follows

Rank	*Annual pay (£)*
Acting surgeon lieutenant/lieutenant/flying-officer	657
Surgeon lieutenant/captain/flight-lieutenant	766–1058
Surgeon lieutenant-commander/major/squadron-leader	1295–1569
Surgeon commander/lieutenant-colonel/wing-commander	1660–1934
Surgeon captain/colonel/group-captain	2080–2244
Surgeon captain after 8 years in the rank/brigadier/air commodore	2354
Surgeon rear-admiral/major-general/air vice-marshal	3029
Surgeon vice-admiral/lieutenant-general/air marshal	3759

REMUNERATION OF PUBLIC-HEALTH DOCTORS

A CLAIM by the staff side of Committee C of the Medical Whitley Council for an increase in the remuneration of public-health doctors from Jan 1, 1958, to take account of the rise in the cost of living since their salaries were last readjusted on April 1, 1956, was rejected by the management side at a meeting of the committee on Feb 11 The two sides have agreed to ask the Ministry of Labour and National Service to refer the difference to the Industrial Court for arbitration. The staff side informed the management side that a claim for a major reform of the remuneration structure of public-health doctors is being prepared and will be lodged with the management side later

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[1] See *Lancet*, 1956, ii, 1221

[2] See *ibid* p 501

[3] ' Operation Regionalisation ' in Puerto Rico Published by the Department of Health, Commonwealth of Puerto Rico San Juan, 1957 Pp 26

[1] McDermott, T J *Electron Engng*, 1958, 30, 65

[2] Service Pay and Allowances Cmd 365 H M Stationery Office Pp 36 2s

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University of Cambridge

On Feb 8 the degree of M B was conferred on the following

L. J Chalstrey, J A Mathews (by proxy), R. S O Rees.

University of London

Dr M L Thomson, senior lecturer at the London School of Hygiene and Tropical Medicine, has been appointed to the readership in applied physiology at the school

The title of professor has been conferred on Dr George Brownlee of King's College (pharmacology), Dr William Robson of King's College (biochemistry), and Dr Miles Weatherall of the London Hospital Medical College (pharmacology), and the title of reader on Dr B E D Cooke of Guy's Hospital Medical School (dental medicine), Dr Harry Harris of the London Hospital Medical College (biochemical genetics), and Dr J P Quilliam of St. Bartholomew's Hospital Medical College (pharmacology)

On Jan. 29 the degree of M.D was conferred on Allan Jacobs

University of Liverpool

Dr C. A Clarke has been appointed to a readership in the department of medicine

Royal College of Surgeons of England

At a meeting of the council on Feb 13, with Sir James Paterson Ross, the president, in the chair, Mr Hugh Reid and Mr A. H M Siddons were elected and Prof Victor Lambert was re-elected to the court of examiners The Hallett prize was awarded to Dr K A Butler A diploma of fellowship was granted to N R Narayan, and diplomas of fellowship in the faculty of anæsthetists to the following

E. J D Arcy, J R. Cross, J W McCloy, Joan K. Perkins, A F Roper, R. M McClelland Shelagh Wimhurst, Brian Dawson, K. H. Oldfield, W W Jones C D Linton J W Mostert D L. Pryer, H C. Newman, Pamela M Paddock, R. G Snow, V A Grimshaw, Brian Kay, A S Paton, Joseph Chaz, E. R. Fawcett, D J Waters, Margot R. Craw, E. R. Lester

Licences to practise and the diplomas mentioned in our issue of Feb 8 (p 327) were conferred jointly with the Royal College of Physicians

Royal College of Physicians of Ireland

At a meeting of the college on Feb 7, with Dr F J O Donnell, the president, in the chair, Jerzy Jozef Biezenski and Patrick Donough Moylan were admitted to the membership

British Medical Association

The annual meeting of the association will be held this year in Birmingham from July 10 to 18

Society of Apothecaries of London

A course of twelve subscription lectures on advanced surgery will be given in the hall of the society, Blackfriars Lane, E C 4, at 5 P.M and 6 15 P.M from March 27 to April 3 Further particulars may be had from the registrar of the society

Hugh Cairns Memorial Lecture

On Friday, March 14, at 5 P.M at the London Hospital, E 1, Sir Geoffrey Jefferson will give the first Cairns lecture to the Society of British Neurological Surgeons He will speak on Sir Hugh Cairns Tickets may be had from Mr D W C. Northfield at the London Hospital

Ciba Foundation

On Wednesday, March 5, at 5 P.M at Manson House, 26, Portland Place, London, W 1, Prof Daniel Bovet will give the foundation's annual lecture His subject will be the experimental basis of neuroleptic and tranquillising therapy Admission is by ticket only, obtainable free from the assistant secretary of the association, 41, Portland Place, W 1.

Freezing and Drying

The Institute of Biology is holding an international symposium on this subject in the Senate House, Malet Street, London, W C.1, on April 1 and 2 Further particulars may be had from the general secretary of the Institute, 41, Queen's Gate, S W 7

Swiney Prize

The next award of this prize will be made in January, 1959, for a work on medical jurisprudence The prize (a cup and £100) is awarded by a joint committee of the Royal Society of Arts and the Royal College of Physicians of London Further particulars may be had from the secretary of the society, John Adam Street, Adelphi, W C 2

Radiation Hazards

The Services group of the Society of Medical Officers of Health is to hold a course on this subject for 100 medical officers from April 10 to 11 in the library of the Royal Microscopical Society, Tavistock House South, London, W C.1 The fee for the course is 4 guineas, and applications should be sent to the secretary of the society at Tavistock House South.

World Health Organisation

Dr Constantin Vinokouroff, department chief at the Neurological Institute of the U S S R. Academy of Medical Sciences, has been appointed director of the Division of Therapeutic Substances at W H O headquarters in succession to Dr W Aeg Timmerman, who last year was appointed assistant director-general in charge of the Department of Central Technical Services

Hunterian Society

With a record attendance of some 300, this society held its annual dinner on Feb 13, which it regards as John Hunter's birthday

Mr Justice Upjohn, proposing its health, learnedly translated its motto, *Ratio Societatis Vinculum*, as " Good-oh, we've got a stranglehold on the people generally" Following the English way of life, by which one has at the top someone who knows absolutely nothing and prefers not to learn, he himself was John Hunter's lineal successor as chairman of St. George's Hospital Medical School Nevertheless he was appalled that so many members of the medical profession, overburdened and overworking, should apparently be obliged to attend so many committee meetings He concluded with a tribute to the president, Mr J C Ainsworth-Davis, by specialty " a hewer of stone and a drawer of water "

Responding, the President described the year's activities, including the ' popular meeting " at which Sir Francis Walshe and Lord Attlee opened a debate on whether a full-time State-controlled medical service is contrary to the best interests of the patient, and the assembly decided by 250 votes to 1 that it would be. Hunter (Mr Ainsworth-Davis hoped) would be gratified to know that his memory is honoured in the society with sincerity and affection

Sir Walter Fergusson Hannay, proposing The Lord Mayor and Corporation, said that the society's founders used to meet in coffee-houses in the City and it still holds its discussion meetings in taverns It enjoyed its unique relations with the City, and the privilege by which the Hunterian oration is annually delivered in the Mansion House The Lord Mayor (Sir Denis Truscott) spoke of his office and its insignia, including a badge made in 1799 which contained (he could tell the President) some very large stones of the finest water

Into his kindly speech on The Guests Lord Evans somehow managed to introduce a good deal about snakes and parasites. He described the Apothecaries Hall as the most delightful place in which to fail an examination, welcomed Mr Dickson Wright particularly as president of several medical societies and—in masterly fashion—of the Harvey Tercentenary Congress, and said that whether British medicine is to thrive or even survive under the National Health Service depends on a sound position for the family doctor Mr Justice Stevenson, in reply, said he was glad that the wave of medical litigation has abated and that one no longer sees doctors who conduct almost the whole of their practice in the witness-box. All the same, as a judge, he could not help greeting as a breath of fresh air, any conflict of medical testimony He was making diligent search for a psychiatrist who could resolve the frustration likely to be set up by listening in silence

Fellowship of Postgraduate Medicine

A course on rheumatic diseases will be held at the Rheumatism Unit, St Stephen's Hospital, Fulham Road, S W 10, on March 15 and 16 Further particulars may be had from the registrar of the unit

Industrial Welfare Society

This society is to hold a conference on industrial health at the Hotel Rembrandt, Thurloe Place, London, S W 7, at 10 A M on Thursday, March 13 The speakers will include Dr T O Garland and Dr F H Tyrer Further details may be had from the Press officer of the society, 48, Bryanston Square, W 1

Cheadle Royal Hospital

The Nuffield Provincial Hospitals Trust has made a grant of £7500, spread over three years towards setting up a sheltered workshop for long-stay patients with chronic psychotic illnesses, and a grant of £1500 for an investigation into the cost of mental illness

Hospital Sterilisation Procedures

The Sheffield Regional Hospital Board is sponsoring a conference on this subject which is to be held at the University of Nottingham on April 2 The chair will be taken by Prof C P Beattie, and the speakers will include Prof J W Howie The conference will be attended by surgeons, pathologists, pharmacists, group engineers, and group secretaries nominated by the hospital management committees in the region

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An association of medical advisers to the pharmaceutical industry has been formed, which will discuss professional topics of common interest at the three or four meetings to be held each year Dr G R Fryers (Clifton House, Euston Road, London, N W 1) is the hon treasurer

The C M F/M E F Physicians' reunion dinner will be held at Simpson's-in-the-Strand, London, W C 2, on Saturday, April 26 Information may be had from Dr A Willcox, 59, Harley-street, W 1

Appointments

Brown, Robert, M D Edin , M R C O G consultant obstetrician and gynæcologist, Tees-side and Cleveland groups of hospitals

*Ferguson, R S , M D Glasg , D P M consultant psychiatrist and deputy medical superintendent, Lancaster Moor Hospital

Horton, R E , M B E , M S Lond , F R C S consultant surgeon, United Bristol Hospitals

Levis, Hilda M , M B Lond , D P H assistant M O , Macclesfield

Patey, D G H , B M Oxon assistant M O , Luton

Phillips, C I , M D Aberd , F R C S , D P H , D O consultant ophthalmic surgeon, United Bristol Hospitals and South-Western Regional Hospital Board

Rees, T A I , M B Lond , D P H , D I H , D C H , D OBST senior M O for maternity and child welfare, Leicester

Smeaton, W G , M B St And , D P H M O H , Peterborough

East Anglian Regional Hospital Board

Joss, G S , M B Aberd registrar in plastic surgery, regional plastic surgery and burns unit, West Norwich Hospital

Tait, I G , M B Camb , D C H registrar in chest medicine, Ipswich chest clinic and St Helen s Hospital, Ipswich

Westbury, D G A , M B Lond registrar in psychiatry, Suffolk Mental Hospitals

Leeds Regional Hospital Board

Berkin, C R., M B Leeds, F R C S part-time consultant in orthopædic surgery, Hull A and East Riding of Yorkshire hospital groups

Bibby, A V G , M B Cantab , M R.C O G part-time consultant in obstetrics and gynæcology, East Riding of Yorkshire hospital group

Cowie, J W , M B Edin , F R C S , D M R D part-time consultant in radiology, Hull area hospitals

Kahn, J H , M D Leeds, D P M part-time consultant in child psychiatry, Harrogate

MacCuish, R K , M B Aberd , M R C P part-time consultant in geriatrics, Bradford

Neville-Smith, C H , B M Oxon , D C.H , D P.M part-time consultant in child psychiatry, York and Scarborough

Wild, A A , M B Edin , D M R D part-time consultant in radiology, Scarborough, Bridlington, and Malton

Wilkinson, N V , M B Durh , D P M assistant psychiatrist (S H M O), Clifton Hospital, York, and associated clinics

Liverpool Regional Hospital Board

Keidan, S E , M B Lpool, M.R C P , D C H part-time pædiatrician Alder Hey Children s Hospital

Stewart, J M A C , M B Birm , D P M assistant psychiatrist, Rainhill Hospital

Tracy Forster, R V , M B Lpool, F R C S , D L O part-time consultant E N T surgeon, Southport Promenade Hospital

* Amended note

Diary of the Week

FEB 23 TO MARCH 1

Monday, 24th

Postgraduate Medical School, Ducane Road, W 12
4 P M Dr Lawson McDonald Aspects of the Assessment for Cardiac Surgery

Manchester Medical Society
9 P M (Medical School, University of Manchester) *General Practice* Dr M T Parker Uses of a Bacteriological Laboratory to General Practitioners

Tuesday, 25th

Royal Society of Medicine, 1, Wimpole Street, W 1
8 P M *Medicine* Dr D V Hubble, Dr R E Steiner, Dr H A Sissons Skeletal Manifestations of General Disease

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Prof C H Stuart-Harris Adenoviruses and Respiratory Disease in Man

St Mary s Hospital Medical School, W 2
5 P M Mr A J Wrigley Postmaturity

Institute of Neurology, Queen Square, W C 1
5 30 P M Prof H Bertha (Graz) Brain Tumour and Cerebral Circulation.

Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr Brian Russell Tuberculosis of the Skin

West End Hospital for Neurology and Neurosurgery, 91, Dean Street, W 1
5 30 P M Mr Joseph Minton Ocular Manifestations in Clinical Neurology (Second of two lectures)

Wednesday, 26th

Postgraduate Medical School
2 P M Prof J H Dible Pathology of Lower Limb Ischæmia

Institute of Diseases of the Chest, Brompton, S W 3
5 P M Mr T Holmes Sellors Surgery of Atrial Septal Defects

Institute of Dermatology
5 30 P M Dr R W Riddell Recent Advances in the Study of Ringworm Infections

British Association of Sport and Medicine
5 45 P M (St George's Hospital, S W 1) Mr Harold Abrahams The Photo Finish Mr W E Tucker Treatment of Sports Injuries

Royal Faculty of Physicians and Surgeons of Glasgow, 242, St Vincent Street, Glasgow
5 P M Dr Jan Brod (Prague) Hæmodynamic Aspects of Hypertension in Relation to the Pathogenesis of the Disease (Burns lecture)

Thursday, 27th

University College, Gower Street, W C 1
5 P M *Biochemistry* Dr F H C Crick The Nucleic Acids—Speculation and Prospects (Last of three lectures)

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine) Prof G W A Dick Poliomyelitis

Institute of Dermatology
5 30 P M Dr P F Borrie Nodular Conditions of the Legs

Liverpool Medical Institution, 114, Mount Pleasant, Liverpool, 3
8 P M Miss Isabella Forshall Affections of the Genital Tract in the Female Child

University of St Andrews, Queen's College, Dundee
5 P M Dr W W Park Significance of Sex Chromatin

Friday, 28th

University of London
5 30 P M (London School of Hygiene and Tropical Medicine) Sir Howard Florey Reaction of the Arterial Wall to Injury

Royal Society of Medicine
3 P M *Pædiatrics* (Hospital for Sick Children, Great Ormond Street, W C 1) Demonstrations
5 P M Dr Bernard Schlesinger, Dr John Platt Follow up of Ulcerative Colitis
8 15 P M *Obstetrics and Gynæcology* Mr Malcolm Donaldson Dr John Burton Mr C J Thurgar Early Diagnosis and Cancer Education of the Public

Postgraduate Medical School
10 A M Mr David Levi Abdominal Pain in Children
4 P M Dr J F Goodwin Peripheral Vascular Disease

Medical Society for the Study of Venereal Diseases, 11, Chandos Street, W 1
7 30 P M Dr S M Laird Figures and Fancies (Presidential address)

British Tuberculosis Association
4 30 P M (26, Portland Place, W 1) Dr Philip Evans, Mr Charles Keogh The Chesty Child

Plymouth Medical Society
8 30 P M (Freedom Fields) Sir Cecil Wakeley Aspects of Malignant Disease

Births, Marriages, and Deaths

BIRTHS

Rose —On Jan 15, to Flora Rose (formerly Macdonald), M B , and B S Rose, M.R C P , of Rotorua, New Zealand—a brother for James and Timothy, Toby Francis

DEATHS

Bickford —On Feb 9, Dr Nicholas Seymour Bickford of Wimbledon aged 83, only surviving child of the late J W F Bickford J P , of Bickington, Devon

The Lancet · Saturday 1 March 1958

UNCONSCIOUSNESS

A CLINICOPATHOLOGICAL STUDY*

MOGENS FOG
M D Copenhagen
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OUR understanding of the mechanisms of consciousness can be prompted by studying unconsciousness

The relationship of consciousness to unconsciousness is not merely that of positive to negative Examining an unconscious patient we only know that, in his present state, one or more elements essential to the maintenance of wakefulness are out of order Even if we can localise the cerebral damage either clinically or post mortem, it is unjustifiable to conclude that the damaged areas alone are responsible for full consciousness

A similar reservation has been repeated with reference to brain functions in general and is undoubtedly true, but it may lead to a sort of nihilism it may lead to our giving up all attempts to draw conclusions, from pathological states and their sites, about the basis of normal behaviour After all, what we learn about the indispensable elements of a function through their extinction must throw at least some light on important factors in their normal performance

Most recent observations which have enriched our insight into the mechanism and morphological correlates of consciousness have been collected by experiments on lower animals and only partly on man Clinicopathological contributions are relatively uncommon and often inconclusive Apart from epilepsy, our clinical studies of consciousness have not taken full account of the physiological discoveries of the past decade, and the physiologists, on the other hand, were scarcely inspired by clinical problems when they tackled this subject It therefore seems desirable to present all the material that may help us to bridge the gap between experimental evidence and neurological experience

The importance of consciousness in modern neurology is clear not only from the overwhelming number of papers published on it but also from the fact that it was a main theme at the Symposium on Brain Mechanisms and Consciousness held in Canada in 1954 and at the first International Congress of Neurological Sciences held in Brussels in 1957

Definition

The term " consciousness " is ambiguous one meaning is the perceptiveness and reactivity of the nervous system, and the other is the content of the conscious mind

Awareness is the basic unspecific function underlying conscious activities as a whole It is presumably connected with the activator system of the reticular formation of the brain-stem, and its tone is maintained both by afferent external and proprioceptive stimuli, as well as by impulses descending from the cortex, and, to some degree, by humoral regulations parallel to chemical regulation of the respiratory and vasomotor centres

The physiological basis of the psychological content of consciousness is unknown but must presumably be sought primarily in the cortex

The complicated ramifications of conscious conduct make it impossible to fix and define consciousness As Hughlings Jackson pointed out, we are differently conscious (in all respects) from one moment to the next (see Taylor et al 1931)

Anatomical Basis of Consciousness

The display of consciousness depends on the action of and interaction within the extended corticosubcortical organisation, which Penfield (1957) has designated " centrencephalic " From neurophysiological observations of the arousal response and from clinical experiments on epilepsy it may be concluded that certain cortical areas have more direct influence than others on this interrelationship the sensorimotor, anterior frontal, occipital, and paraoccipital cortex, the upper temporal gyrus, the tip of the temporal lobe, the uncus, the cingulate gyrus, and the frontal oculomotor region (French 1957, Penfield 1957)

No single cortical area is essential for the maintenance of consciousness (Penfield 1957), but, if the cortical connections with the subcortical organisation subserving awareness are disrupted, both awareness and the contents of the conscious mind are abolished (Alajouanine 1957)

In the subcortical part of the brain special importance must be ascribed to the reticular formation in the caudal mesencephalon, the trigeminal and intercollicular regions (Bremer 1957), and (as the ultimate relays of reticulo-cortical connections) the nonspecific interlaminar, reticular, and anterior ventral thalamic nuclei (Morison and Dempsey 1942, Hanberry and Jasper 1953, Hanberry et al 1954)

There are many reasons for the relative scarcity of clinicopathological contributions in this field Such approaches must be based on an inadequate negative correlation to the normal function they are perforce based on unconsciousness—a term which only describes some degree of reduced responsiveness, reduced reactivity to outer and inner stimuli Furthermore, the ideal demands which pathological material must satisfy if it is to be conclusive are too rigorous to be fulfilled in practice

(1) Unconsciousness must be the predominant feature of the clinical state before death

(2) The lesions produced by the fatal disease must be distinctly localised and discernible in the brain Gross injuries and diffuse damage will not allow specific deductions

(3) Unconsciousness must have lasted long enough to produce peculiar pathological changes, but not so long that most cerebral elements are in an equal state of degeneration

(4) Finally, one must take into consideration the fact that we cannot yet distinguish with certainty between neuronal impairment due to primary effects of the ætiological factor and axonal, retrograde, and transneuronal degeneration

For the time being, therefore, we can draw only modest conclusions from clinicopathological studies They may nevertheless provide some indications about how we are to achieve closer insight into consciousness in man, and they suggest further lines of investigation

Case-reports

The following case-reports illustrate the effects of prolonged fatal unconsciousness None of the cases fulfils all the criteria mentioned above, and none has

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* A lecture delivered at the National Hospital, Queen Square, London on Oct 11, 1957

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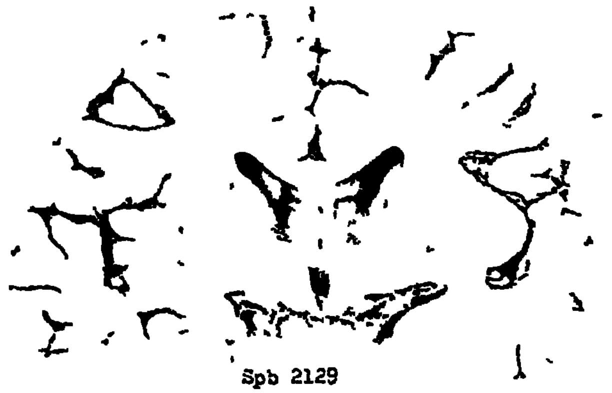

Fig 1—Case 1 frontal section of brain, showing diffuse cortical atrophy

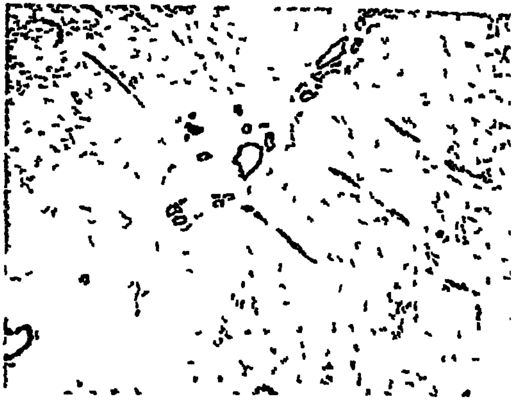

Fig 2—Case 1 pseudolaminar degeneration of calcarine

yet been adequately examined They can only serve as examples

Case 1 —A man, aged 67, was admitted to hospital shortly after his schizophrenic son had tried to strangle him He was unconscious, with strangulation marks round his neck and with conjunctival hæmorrhages He remained unconscious for 47 days and then died During this time his temperature, blood-pressure, respiration, diuresis, and defæcation were normal, his right pupil sometimes reacted to light, but his left did not, and both were in medium contraction, he had no corneal reflexes and no conjugated deviation of the eyes, but he had swimming bulbar movements, subtotal paresis of both facial nerves, decerebrate rigidity, and incomplete tonic neck reflexes, especially when his head was turned towards the left Unilateral flexor reflexes of the lower extremities were easily provoked

Electro-encephalography one week and three weeks after admission showed no alpha rhythm and no slow frequency On the first occasion only there was some 26-per-sec activity with an amplitude of 5-10 mV in the right occipital region

Necropsy findings †—The brain, after fixation, weighed 1200 g The leptomeninges were slightly œdematous, there were no hæmorrhages and no sclerosis or thrombosis of the vessels The main finding was severe diffuse atrophy of the cortex, with macroscopic necrosis in the occipital lobes (fig 1) Histologically the lesions were pseudolaminar necrosis in the frontal and motor regions and total necrosis in the occipital areas The necrotic foci were surrounded by proliferated vessels and fibrillary and gemistocytic astrocytes The remaining nerve-cells were anoxic, showing chromatolysis and pyknotic nuclei (fig 2) In the white subcortical matter the fibres were demyelinated, otherwise the white matt intact There were confluent perivascular degenerati in the corpus striatum, mainly affecting the caudate putamina, and claustra (fig 3) The globi pallidi r only slight degeneration of the nerve-cells, and the red were affected, especially on the left side The cere showed severe degeneration of the Purkinje cells a dentate nuclei

Comments

In this case of acute anoxia the primary an dominant lesions were in the cortex, especially visual and precentral regions, and in the caudat lenticular nuclei

This localisation is in accordance with the conc (Himwich 1949) that, in anoxia, the "highest le (Hughlings Jackson 1931) of cerebral organisatio affected first and most severely

From his observations of the progressive sym during acute anoxia and nitrogen inhalation Hi (1949) has deduced that they depict gradual r phenomena from (1) the cortex (visual disturb unconsciousness, motor restlessness), (2) the ganglia (torsion, spasms), (3) mesencephalon (o tonus), and (4) *lower brain-stem (embryotonus)*

No account can be given of the initial state of c but the main localisation of the cerebral damage ind convincingly that his prolonged unconsciousness w result of primary diffuse degeneration of the corte

The lesions were especially severe in the motor calcarine regions These are the most vascula

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† Dr Erna Christensen made all the pathological examinations

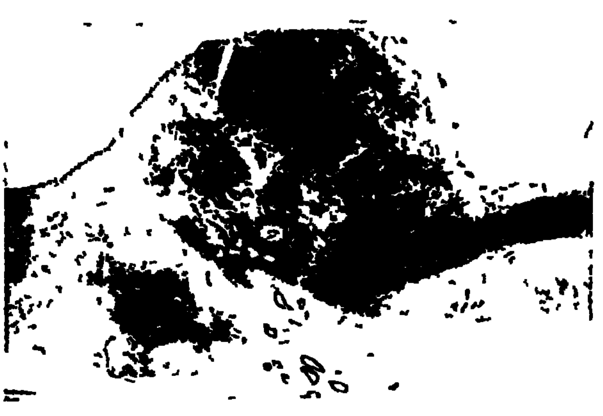

Fig 3—Case 1 frontal section through basal ganglia at anterior commissure, showing degenerative foci in caudate nucleus and putamen

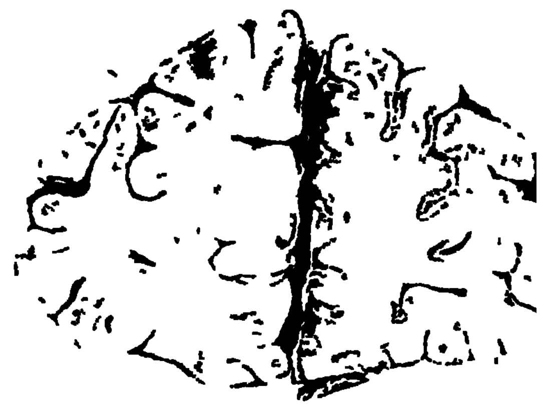

Fig 4—Case 2 frontal section of brain, showing multiple are necrosis and softening of cortex

parts of the cortex, which fact presumably signifies that their need of oxygen is greater than that of other parts of the cortex Therefore these areas are the most vulnerable when exposed to anoxia (Courville 1953)

The greatest damage in the basal ganglia was in the neostriatum, the putamen, and the caudate nucleus

Case 1 therefore presents typical lesions of anoxia in agreement with the conception that the highest cerebral levels are the most vulnerable

Now, as already mentioned, experiments show that the maintenance of consciousness depends on the relationship between the cortex and the subcortical activator systems—a sort of feedback from the cortex to the reticular formation and from these structures corticopetally Therefore the question arises when a person is unconscious for a long time because of an extended cortical lesion, will parts of the reticular formation degenerate because of inactivity or postneuronal or retrograde degeneration?

The pathways from the reticular system to the cortex are undoubtedly multineuronal Quite how many links the neuronal chain contains is unknown, but presumably the last station, or one of the last stations, must be in the ventrolateral and reticular nuclei of the thalamus

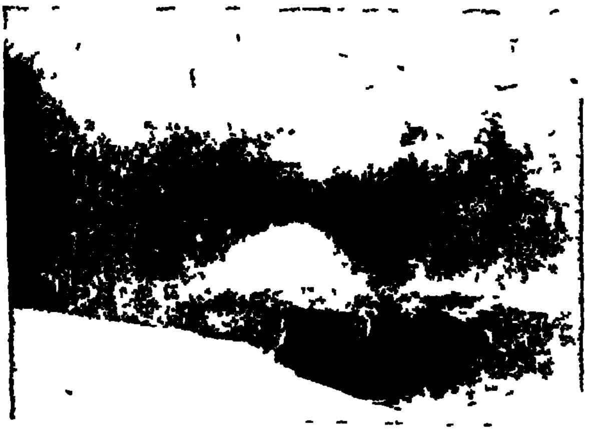

Fig 5—Case 2 thalamus at posterior commissure, showing encephalomalacia involving dorsomedial and interlaminar nuclei

It is regrettable that, in case 1, no histological preparations were preserved to allow more careful study of these structures, but it was noted that the thalamus presented no distinct alterations On the other hand, examination of the reticular nuclei of the mesencephalon, the pons, and the medulla revealed no distinct alterations in the cells of the central matter or of the cranial-nerve nuclei

Thus it is shown that prolonged unconsciousness provoked by cortical and neostriate degeneration does not necessarily lead to secondary histological involvement of the mesencephalon and caudal reticular formation

Case 2—A mentally depressed woman, aged 47, threw herself out of a window and was admitted to hospital unconscious She had two general convulsive fits and was transferred to a neurosurgical clinic She reacted to pain, her pupils were contracted and did not react to light, and her legs were extended and spastic She had no spasticity of her arms and no facial paresis Surgical exploration disclosed a subdural hæmatoma and a contusion of the right occipital lobe

For some weeks the patient remained unconscious, with frequent brain-stem attacks Her respiration and blood-pressure were normal The tone of her limbs and her tendon-reflexes gradually disappeared She developed uræmia and died after 31 days

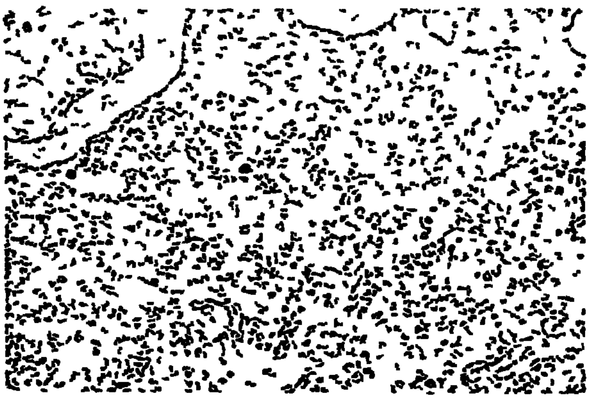

Fig 6—Case 2 brain-stem at fifth nerve nucleus, showing degeneration and vascular stasis in reticular nuclei

Necropsy findings—There were remnants of the subdural hæmatoma over the right hemisphere, but otherwise no extracerebral bleeding The cortex was the site of multiple foci of necrosis and softening of various extent (fig 4) Histological examination showed laminar degeneration with proliferation of astrocytes, macrophages, and localised collections of multinuclear giant cells In the thalamus there was an irregular encephalomalacic cystic lesion in the dorsomedial nucleus, involving the internal laminar area (fig 5) The cellular reactions of the surroundings were similar to those of the cortex The brain-stem contained many fresh degenerative lesions At the level of the fifth-nerve nucleus in the pons was a distinct necrosis localised to the reticular formation of one side (fig 6) Both the cells and the myelin sheaths were totally degenerated, comparison with the cortical lesions giving the impression that the brain-stem lesions were of recent origin There were only a few macrophages The medulla likewise showed unilateral but not total degeneration of the reticular formation

Comments

The primary cause of unconsciousness in this case was presumably the extensive necrosis in the cortex, possibly due to acute vascular paralysis caused by the head trauma The cystic necrosis of the thalamus, however, also bears the stamp of an old and presumably initial lesion These telencephalic and diencephalic findings contrast indisputably with the fresh character of the alterations in the brain-stem

Would it be too rash to assume that these degenerations of the reticular formation of the lower brain-stem

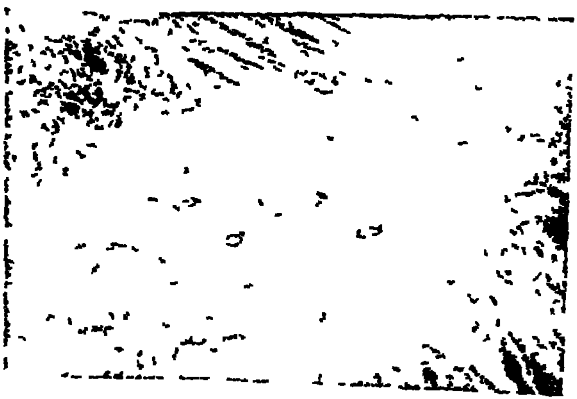

Fig 7—Case 3 pallidal globe showing perivascular confluent necroses with cystic degeneration

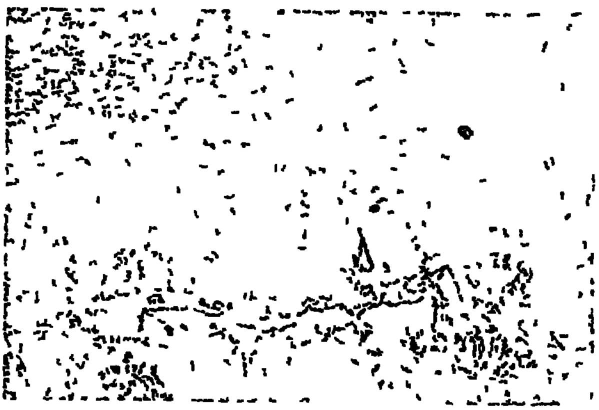

Fig 8—Case 3 cerebellar cortex, showing severe degeneration with disappearance of Purkinje cells, molecular layer, and patches of granular layer

were secondary to the damage at a higher level, especially that in the thalamus in structures which we assume act in close connection with the lower activating system?

Although the thalamic nuclei were not examined in detail in case 1, at least there were no conspicuous lesions Further studies are necessary to decide whether an exclusively cortical necrosis can lead to reticular damage in the brain-stem, or whether thalamic involvement is a necessary precursor of such secondary degeneration

Case 3—A woman, aged 54, was given two injections of morphine for vesical tenesmus She fell asleep and was found unconscious $4^1/_2$ hours later A doctor was called and removed her false teeth, which had slipped into her pharynx The patient was cyanotic, unconscious, and in a state of shock, with a low blood-pressure of 80 mm Hg, dropping to 35 mm Her pupils were of medium size and did not react to light She had flaccid paresis of all her limbs, and no tendon and plantar reflexes During the following 24 hours she reacted to sounds several times Occasionally she coughed and swallowed during tracheal suction, and once she said "outch" when her arms were raised above her head Spasticity and rigidity developed later, and the patient had several brain-stem attacks, either spontaneous or provoked by touching and pricking Her condition deteriorated slowly until death $7^1/_2$ weeks after the initial suffocation

Necropsy findings—No external abnormalities were observed apart from slight œdema of the brain and leptomeninges On coronal section both globi pallidi were seen to be completely necrotic, and the cerebellar cortex presented various degrees of atrophy Histological examination of the cortical grey matter disclosed various degrees of anoxic degeneration with pyknosis, chromatolysis, and shrinking of the cytoplasm

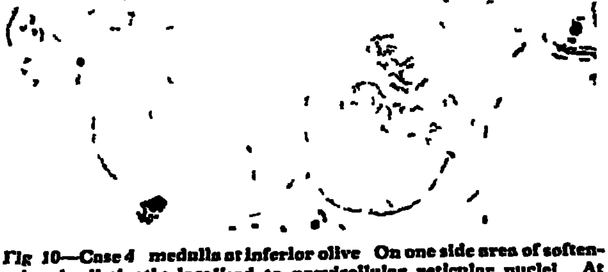

Fig 10—Case 4 medulla at inferior olive On one side area of softening is distinctly localised to parvicellular reticular nuclei At corresponding position on opposite side there is vascular stasis

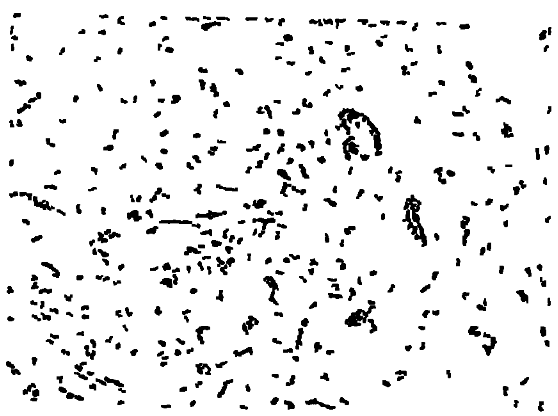

Fig 9—Case 3 lower pons, showing focal necroses in reticular area around dilated vessels, ganglion cells of surrounding nuclei are more or less anoxic

There was no necrosis or glial proliferation In the globi pallidi the arteries were calcified and fibrotic and had a narrow lumen The arterioles were hyaline There were extensive perivascular confluent areas of necrosis with cystic degeneration and deposits of lipoid-containing macrophages (fig 7) The other parts of the basal ganglia, the thalamus, the hypothalamus, and the red nuclei did not show any necrosis, but there were chromophobia of the nerve-cells and stasis in the vessels There were foci of severe degeneration of the cortex in the cerebellum, the Purkinje layer, the molecular stratum, and patches of the granular stratum were destroyed (fig 8) There were deposits of macrophages containing lipid and blood The vessels were narrow and hyaline The white matter and the dentate nuclei presented demyelinisation and anoxic changes In the mesencephalon, pons, and medulla small necrotic perivascular foci were situated in the reticular formation around dilated vessels, while the cells of other nuclei were relatively well preserved The reticular degeneration was bilateral and symmetrical (fig 9)

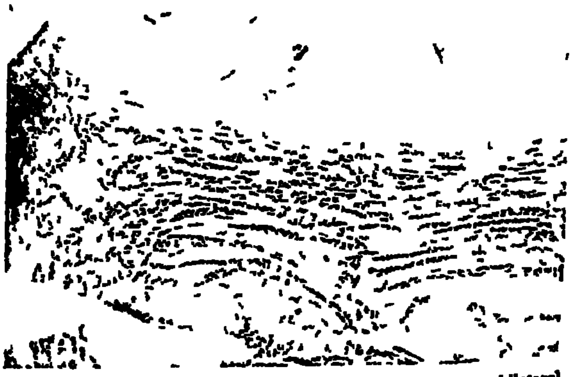

Fig 11—Case 4 upper pons at fifth-nerve nuclei, showing bilateral total destruction involving parvicellular nuclei and ascending mesencephalic tract of fifth nerve

Comments

The most conspicuous feature in this case is the site of the predominant degenerations, which differs much from the sites in case 1 The palæostriatum and the cerebellar cortex were extensively damaged, whereas the cortical structures, even in the calcarine region, were comparatively much better preserved

The difference between the pathogenic factors in these two cases does not convincingly explain the obviously different sites of the main lesions Presumably the anoxia developed more slowly in case 3 than in case 1 Yet, so far as I can see, there is no evidence that such a difference should lead to discrepancies in the localisation of the anoxic lesions So case 3 challenges the hypothesis that degeneration progresses systematically from the highest to the lower cerebral structures during anoxia

Perhaps the arterial sclerosis of the basal and cerebellar regions present in case 3 predisposed to the predominant localisation of the lesions

It still remains to study more closely the relationship between the pathological mechanisms of anoxia, asphyxia, &c and the corresponding distribution of cerebral lesions

In the reticular formation in case 3 were scattered focal degenerations in the mesencephalon, the pons, and the medulla

There was a striking difference between the degeneration of these structures and the relative conservation of the cranial-nerve nuclei It suggests that the involvement of the reticular system must be a specific "sign" It is regrettable that no detailed study was made of the thalamic nuclei, but it was ascertained that no gross necrosis had taken place

The structural basis of unconsciousness in this patient cannot be decided Experimental lesions of the cerebellum and the lenticular striatum do not produce unconsciousness We know very little about the connections between the basal ganglia and the brain-stem's reticular substance, and it seems rather artificial to regard the cortical and mesencephalic bulbar lesions as secondary to the predominant lesions in the pallidum

On the other hand, connections between cerebellar and reticular brain-stem structures have been well established in various animals (Brodal 1957) It would, however, be premature to conclude that in this case the cerebellar lesions were primary, deciding secondarily the degenerations of the reticular nuclei of the bulb The available clinicopathological data do not yet allow us to draw any definite conclusions in this respect

In trying to explain the prolonged lack of consciousness in case 3, two possibilities must be borne in mind either the cortical or the reticular lesions are responsible or unconsciousness may be the joint result of both

Case 4—A boy, aged 9 years, was admitted to hospital as a case of poliomyelitis-polioencephalitis after a week's illness He could still react to commands, but grew more and more torpid and delirious He had stiffness of his neck and back His temperature was above 104°F His cerebrospinal fluid was slightly hæmorrhagic (apparently due to the puncture) with about 50 cells per sq mm (monocytes 50%), the protein content was not determined No paresis was found, the abdominal and tendon reflexes were present, except for the right biceps reflex The patient became completely unconscious after two days and remained so until he died three weeks after admission His temperature remained high, he was cyanotic on several occasions and had to be ventilated by the manual-bag method of positive-pressure ventilation because of moderate varying respiratory insufficiency Uræmia developed during the terminal phase

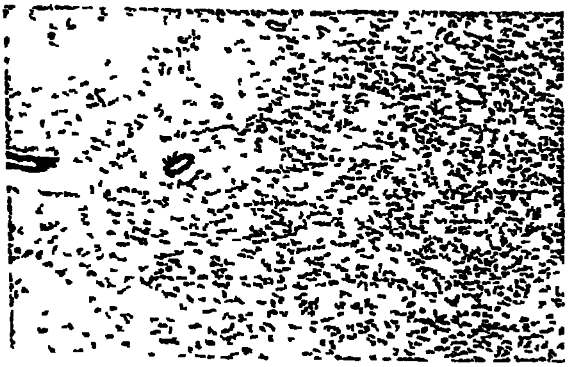

Fig 12—Case 4: thalamus behind corpora mamillaria, showing nerve-cell degeneration, œdema and hæmorrhages corresponding to interlaminar cell-groups; cells of medial and lateral nuclei much less affected

Necropsy findings—There were no signs of poliomyelitis-encephalitis The motor cells of the brain-stem and the spinal medulla were unaffected, and no inflammatory cell reactions were detected In the cortex the ganglion cells were in different stages, varying from normal to atrophic, with glial proliferation—a picture of damage due to anoxia The precise nature of the presumably infectious disease that produced unconsciousness, pyrexia, and respiratory insufficiency was not ascertained The main pathological changes were found in the reticular formation of the brain-stem In the lowest part of the medulla there was no degeneration, but ascending from the level of the eighth nerve there was a clearly defined unilateral softening in the region behind the inferior olive comprising the parvicellular reticular nuclei The corresponding area on the opposite side showed stasis but no total cell degeneration (fig 10) When traced rostrally to the level of the trigeminal nuclei of the pons, totally degenerated symmetrical foci were found medial to the brachium conjunctivum in the parvicellular nuclei and invading the ascending mesencephalic root of the trigeminal nucleus (fig 11) In the mesencephalon, just below the inferior colliculus, the lesions were not so severe as those in the more caudal parts of the brain-stem In the cœrulic nucleus and the medial central grey matter, corresponding to the oral pontine reticular nucleus, the ganglion cells were swollen, chromatolytic, or degenerated Stasis and œdema were also present in this region The thalamus likewise revealed distinct changes In a coronal section just behind the mamillary body, nerve-cell degeneration with œdema and hæmorrhages was conspicuous but confined to the interlaminar cell groups, while the cells in the medial and lateral nuclei were much better preserved (fig 12) The reticular nuclei were likewise relatively unaffected

Comments

These findings are very instructive and unusual The patient's symptoms must be ascribed primarily to the lesions in the reticular formation In view of the different stages of degeneration, the lesions of the parvicellular reticular nuclei of the upper medulla and pons may be regarded as the primary ones Rostrally the damage gradually fades away, so to speak, through the mesencephalon into the thalamus, in which it is localised primarily to the interlaminar nuclei in the rearmost regions, disappearing in the frontal parts of the thalamic regions

In the mesencephalon the cœrulic nucleus was damaged This nucleus is regarded as an important part of a pneumotaxic centre (Baxter and Olszewsky 1955), whereas the parvicellular cell groups of the pons and medulla, to which the main lesions were restricted, are supposed to serve associative functions and to inhibit inspiratory movements (Brodal 1957) These lesions may explain the respiratory failure, but it is remarkable that the failure was not severe

The lack of consciousness, however, must presumably have been due to the supposedly primary lesions in the reticular formation

If one dares to venture further conclusions from the pathological data, it is tempting to regard the laminar degeneration of the thalamus as secondary to the brain-stem reticular softening If this is true, it may tentatively be interpreted as indicating that the first thalamic relay station of the ascending activator system in the thalamus is situated in these structures It has already been mentioned that Hanberry et al (Hanberry and Jasper 1953, Hanberry et al 1954) concluded from experimental data that the lateral ventral thalamic nuclei are the final relay stations for the stimuli determining the awareness of the cortex

In two other cases the necropsies, though incomplete, were informative

Case 5.—A man, aged 44, had 3 years' history of brain-stem attacks with vertigo, vomiting, and nystagmus, transient oculomotor paresis, unilateral palate paresis, Horner's syndrome, &c , all remitting Immediately after one of the fits of giddiness he lost consciousness and was admitted to hospital When I saw him two days later, he lay with open eyes, and his gaze followed my movements From his look I judged that he recognised me (I had treated him for some years) and kept track of the examination His wife likewise had the impression that he was not unconscious but observed what went on around him and to some extent understood what happened He made no spontaneous movements apart from turning his eyes Usually his head was turned to the right, but he occasionally turned it to the left He had general hypotonia, weak tendon-reflexes, extensor plantar responses, no tonic neck-reflexes, and normal respiration He died 14 days after his "stroke"

Necropsy revealed atheromatosis of the basilar artery with a recent partial thrombosis There was fresh softening in the pons, comprising the dorsal half of the cross-section and extending about 3 cm in the caudal-oral direction, presumably from the fifth nuclei towards the medulla

Case 6—A woman, aged 24, collapsed during delivery and lost consciousness After two attacks of general convulsions she remained without spontaneous motion and deeply unconscious for 50 days before she died Neurological examination 4 weeks after her collapse elicited facial contractions when she was pricked on the face, trunk, and limbs No other motor action was observed, and her limbs were hypotonic All her tendon-reflexes were present but weak, her plantar responses were extensor No tonic neck-reflexes were evoked

Necropsy disclosed widespread hæmorrhagic softening invading the dorsal parts of the pons and extending caudally to the upper part of the medulla and orally to the lower mesencephalon

Comments

Case 5 presented a lesion confined to the pontine structures and a clinical state which somewhat resembled what Cairns (1941) called "akinetic mutism" In case 6 prolonged unconsciousness was correlated to a similarly situated softening, which, however, extended *into* the lower mesencephalon

In comparing these two cases one is reminded of Bremer's (1935) experiments on the *cerveau isolé* and those of Roger et al (1956) on the *encéphale isolé* These studies seem to demonstrate convincingly that the trigeminal afferent impulses and nuclei and the mesencephalic intercollicular region are of special importance for maintaining consciousness or awareness Consciousness is definitely impaired if a section is made between the pons and the mesencephalon (*cerveau isolé*), and it is at least partially preserved—oscillating between wakefulness and sleep—when only the ascending reticular formation and fifth-nerve pathways from the pontine to the mesencephalic areas remain intact, while other ascending afferent pathways are interrupted

It would lead too far to consider these problems in detail, but cases 5 and 6 show that the experimental and the clinical observations may correspond closely

Discussion

Few, if any, definite and detailed conclusions can be drawn from these six cases of prolonged unconsciousness The following, however, may be justifiable

(1) Unconsciousness is a consequence of extensive destruction of the cortical grey matter (cases 1 and 2)—which is not surprising

(2) Unconsciousness may be the result of a lesion arising *primarily* in the brain-stem reticular formation and predominantly localised there (case 4)

(3) Diffuse severe cortical atrophy does not necessarily lead to degeneration of the brain-stem reticular formation (case 1), even if unconsciousness is prolonged for several weeks

(4) In case 2 with cortical atrophy, in whom the thalamus was also damaged (the dorsomedial and, conceivably, the interlaminar nuclei), fresh and therefore possibly secondary degeneration was found in the reticular nuclei of the brain stem

(5) In anoxia followed by prolonged unconsciousness the basal ganglia, the globi pallidi, and the cerebellar cortex can be more severely affected than the cortical grey matter (case 3)

(6) Fresh involvement of the bulbar reticular formation was observed when the globi pallidi and cerebellar cortex seemed to be the seat of the most profuse and primary lesions (case 3)

(7) Some data indicate that the interlaminar thalamic nuclei act as the main neuronal relay station for the ascending activator (or some other) reticular function (case 4)

(8) Lesions in the pons at and below the level of the main fifth-nerve nuclei may lead to immobility with apparent preservation of some sort of awareness, whereas low mesencephalic lesions are incompatible with conscious conduct (cases 5 and 6)

Thus even rough clinicopathological observations confirm some recent experimental results concerning the mechanisms of consciousness

We have still to collect further cases which have been thoroughly examined both before death and histologically with special regard to the minute distribution of degenerative lesions present in the different structures of the various levels of the central nervous system involved in conscious processes Such studies will contribute to the correlation of clinical and experimental data concerning the structural differentiation of the functions of the activating and inhibiting reticular system

Purdon Martin (1949) stated that what we call consciousness is unconditionally connected with cortical activity This statement was made when the study of the physiology of the reticular formation was only just beginning It is undoubtedly true of the full display of conscious conduct, but whether the basic function of awareness also necessarily involves the cortex in man is still uncertain

The fact that only apparently late and moderate damage was found in case 4, where the reticular formation was the site of primary and predominant lesions, does not exclude an early functional disorder of the cortical grey matter After all, histological methods presumably do not reveal the first stages of impaired function

It will be of utmost interest, in the attempt to assess the respective roles of cortical and subcortical activities, to compare electroencephalograms in unconscious patients with the postmortem demonstration of primary and secondary lesions of the different structures which today we consider to be involved in the maintenance of consciousness

We have taken but the first hesitating steps towards understanding this basic function of the human brain—a fundamental problem of neurology

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RESPIRATORY COMPLICATIONS OF INFLUENZA

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THOUGH the recent epidemic of Asian influenza in this country has, in general, been mild, many patients have needed admission to hospital on account of respiratory complications Over a period of six weeks, between the end of September and the beginning of November, 1957, 125 such patients were admitted to three hospitals in Edinburgh and this report is a summary of our experience in their management

Clinical Material

Patients were included in this report only if they had symptoms suggestive of influenza either at the onset of the illness for which they were referred to hospital or during the preceding two weeks Because many patients were admitted in a comparatively short period virus studies could be done in only a sample (12 cases) at the beginning of the epidemic, but in all these positive serological evidence of recent influenza (type A, Asian strain) was obtained It therefore seemed reasonable to assume on clinical evidence alone that the remaining patients also had influenza

Of the 125 patients, 63 were male and 62 female For the purpose of this report they have been classified, according to clinical and radiographic features, into the following three groups (1) laryngotracheitis, (2) bronchitis/bronchiolitis, and (3) pneumonia

TABLE I—CLINICAL/RADIOGRAPHIC CLASSIFICATION SHOWING NUMBERS IN EACH GROUP

Type of case	Without chronic respiratory disease	With chronic respiratory disease	Total
Laryngotracheitis	10	4	14
Bronchitis/bronchiolitis	7	35	42
Pneumonia			
Lobar/segmental	17	11	28 } 69
Lobular	18	23	41 }
	52	73	125

All patients with radiographic evidence of pulmonary consolidation have been included in group 3, and they have been subdivided according to the radiographic appearances into those with lobar or segmental lesions and those with lobular lesions The criteria for inclusion in group 1 or 2 were entirely clinical Patients with features of more than one group were classified according to their dominant lesion The numbers are shown in table I 73 patients (58%) had chronic respiratory disease, 2 had bronchial asthma, 2 had bronchiectasis, 11 had clinically significant pulmonary tuberculosis (which was associated with chronic bronchitis in 4), 1 had honeycomb lungs, 1 had diffuse interstitial pulmonary fibrosis of the type described by Hamman and Rich, and the remaining 56 had chronic bronchitis with or without emphysema

Laryngotracheitis Group

Of the 5 male and 9 female patients in this group, 4 had chronic respiratory disease Their ages ranged from 9 years to 67, 9 were aged 30 years or less They all presented with hoarseness, retrosternal pain, and an irritating cough, which was usually dry but occasionally produced scanty tenacious sputum that was sometimes bloodstained 6 had, in addition, evidence of respiratory obstruction, in that after paroxysms of coughing they became intensely breathless and deeply cyanosed, though between paroxysms the airway was adequate All the patients classified in this group responded satisfactorily to treatment in the course of a few days, but 2 other patients, who presented the same clinical picture on admission, later developed pulmonary complications despite treatment—fulminating staphylococcal lobular pneumonia in 1 case and mild segmental pneumonia in the other

Bronchitis/bronchiolitis Group

There were 23 males and 19 females in this group Their ages ranged from 18 years to 80, 30 were over 50 31 (74%) had chronic bronchitis (associated with pulmonary tuberculosis in 4), 3 had quiescent or arrested pulmonary tuberculosis, and 1 had the Hamman-Rich type of diffuse interstitial fibrosis Of the patients with chronic bronchitis, the clinical picture in 29 was indistinguishable from a typical infective exacerbation, though in some, cases the symptoms were more severe, pyrexia higher, and recovery more protracted The 3 patients with pulmonary tuberculosis alone, and 6 of those previously healthy, had acute bronchitis of moderate severity, which responded rapidly to treatment The remaining 4—one without previous respiratory disease, 2 with chronic bronchitis, and the patient with diffuse pulmonary fibrosis—were more acutely ill Dyspnœa, cyanosis, and prostration were prominent features in their illness, which clinically was very similar to lobular pneumonia In 1 case the severity of the clinical picture was little short of that produced by fulminating pneumonia (see below) There was no radiographic evidence of pulmonary consolidation in any of these patients, who were therefore regarded as having bronchiolitis In 3 of them the causal organism was *Staphylococcus pyogenes*

Pneumonia Group

35 males and 34 females had pneumonia 33 were over the age of 60 and 2 under 20 The remainder were evenly distributed within the intervening decades The lesions were lobar or segmental in 28 patients Of these, 11 (39%) had previously had respiratory disease—10 chronic bronchitis and 1 bronchial asthma 41 patients had lobular lesions Of these, 23 (56%) gave a history of previous respiratory disease, 16 had chronic bronchitis, 2 bronchiectasis, and 5 pulmonary tuberculosis (inactive in 4), which was associated with chronic bronchitis in 1

Apart from the duration of pyrexia, which was often longer than expected, the clinical picture in most patients with pneumonia did not differ significantly from that seen at other times. In about a fifth of the 69 cases, however, the illness was much more severe than that commonly encountered apart from an influenza epidemic The most gravely afflicted were 6 patients with fulminating staphylococcal lobular pneumonia, they are considered in more detail below In the others the most striking single feature was the extent of the lesions (massive bilateral consolidation was fairly common), and in rapidity of onset and degree of toxæmia these patients were, in fact, little short of the fulminating group The only 2 pregnant patients in the series had very extensive pulmonary consolidation

In the 6 patients with fulminating staphylococcal lobular pneumonia the initial symptoms of influenza were rapidly followed by hoarseness, retrosternal pain, cough, intense dyspnœa, central cyanosis, and profound prostration The illness in 3 patients was similar to descriptions of fulminating pneumonia complicating influenza recorded in previous epidemics (Scadding 1937, Tyrrell 1952, Stuart-Harris 1953) In the other 3 cases, however, the clinical picture was dominated by signs of respiratory obstruction The 1st, a boy, aged 16, who had severe obstructive symptoms and mediastinal and subcutaneous emphysema, died seven hours after admission to hospital, necropsy showing almost complete obstruction of the trachea and bronchi by membranous mucosal sloughs In the other 2 patients (women aged 23 and 35), both of whom recovered, similar pathological changes were seen in the trachea at bronchoscopy

All these 6 patients had extensive pulmonary consolidation, 1 had massive involvement of both lungs

Bacteriology

In about 40% of the 125 cases an antibiotic, most commonly penicillin, had been given for one to four days before admission to hospital, and this no doubt influenced the results of initial bacteriological examination In 68 cases no specific organism was isolated Predominant organisms in the pre-treatment sputum specimens were reported in the other 57 cases as follows

Pneumococcus	15
Hæmophilus influenzæ	8
Pneumococcus + *H influenzæ*	2
H influenzæ + *Streptococcus pyogenes*	1
Pneumococcus + *Staph pyogenes*	2
Staph pyogenes	29

The cases in which a predominant organism other than *Staph pyogenes* was isolated were distributed fairly evenly throughout the different clinical/radiographic groups Of 31 cases where *Staph pyogenes* was obtained on culture, however, 22 (71%) had pneumonia—lobar or segmental in 9 and lobular in 13 Moreover, *Staph pyogenes* was isolated in all the 6 fulminating cases and from 9 of the 15 patients who died Of 22 patients with staphylococcal pneumonia only 8 (36%) had a previous history of chronic respiratory disease, compared with 58% in the series as a whole

The sensitivities to penicillin, streptomycin, chloramphenicol, tetracycline, and erythromycin of *Staph pyogenes* isolated on admission in 31 cases are shown in table II

TABLE II—SENSITIVITIES OF *Staph pyogenes* ISOLATED ON ADMISSION IN 31 CASES

Antibiotic	Sensitivity					
Penicillin	S	R	S	R	R	R
Streptomycin	S	S	R	S	R	R
Chloramphenicol	S	S	S	S	S	R
Tetracycline	S	S	S	R	R	R
Erythromycin	S	S	S	S	S	S
Totals	14	11	1	1	3	1

S, sensitive R, resistant

Only 45% of the *Staph pyogenes* isolated were sensitive to penicillin Of the penicillin-resistant strains, 75% (12 of 16) were sensitive to streptomycin, 94% (15 of 16) were sensitive to chloramphenicol, 75% (12 of 16) were sensitive to tetracycline, and all were sensitive to erythromycin

Superinfection with staphylococci was believed to have occurred in 12 patients 4 of these had *Staph pyogenes* on admission, but after several days of treatment, and after an intervening sputum specimen had shown no growth or only mixed respiratory organisms, *Staph pyogenes* with different sensitivities from the original was cultured *Staph pyogenes* appeared later in 8 other patients who had originally either mixed respiratory organisms o a pathogen other than *Staph pyogenes* on primary sputum culture

In 3 patients with superinfection the organism was sensitive to erythromycin only A source of the organism in these 3 cases was found in a patient with chronic bronchitis who had been in hospital for several months before the epidemic and who had been given courses of the commoner antibiotics for recurring respiratory infection 2 of these patients died, the 3rd survived a series of catastrophes

In the other cases of superinfection with *Staph pyogenes*, this was not associated with apparent clinical deterioration

Treatment

Antibiotics

When the severity of the pulmonary complications in the present epidemic was appreciated, at first we used a combination of penicillin, streptomycin, and chloramphenicol as primary treatment in the more severe cases

Penicillin and streptomycin were given to combat the commoner organisms, including *H influenzæ* which was considered likely to be an important pathogen Chloramphenicol was included because *Staph pyogenes* was common in severe cases and because we believed that drug resistance would be rare in view of the relatively restricted use of chloramphenicol in this country But superinfection with *Staph pyogenes* followed this regime, and the impression was gained that the broad spectrum of antibacterial effect led to the development of an ecological vacuum in which the now ubiquitous staphylococcus became established It was therefore decided in the latter part of the epidemic to restrict antibiotic treatment to an effective minimum as soon as the sensitivities of any dominant organism in the pre-treatment specimen were known A combination of penicillin and streptomycin has become our standard initial treatment in all but the most seriously ill patients

The combination of penicillin, streptomycin, and chloramphenicol was used in 33 patients, most of whom were treated during the early part of the epidemic Later, chloramphenicol was occasionally given to seriously ill patients, but was always withdrawn whenever sensitivity tests showed that it was no longer needed 51 patients were treated with penicillin plus streptomycin 17 patients received penicillin alone, most of these being mild cases at the beginning of the epidemic

Erythromycin was given, in addition to penicillin and streptomycin, to 6 patients with severe infection In 2 cases its use was dictated by sensitivity tests, but in 4 the illness was so severe that we gave the drug before we had bacteriological evidence that it was needed. The final policy for the critically ill patient was to use penicillin, streptomycin, and erythromycin initially, withdrawing erythromycin as soon as sensitivity tests showed that this was permissible. As far as possible, patients receiving erythromycin were nursed in isolation, with full precautions against cross-infection.

18 patients in the present series had different antibiotic treatment: 6 patients had penicillin and chloramphenicol, 4 chloramphenicol alone, and 8 tetracycline alone. These patients were seen before a treatment policy had been fully formulated, and the treatment was often a continuation of that begun before admission. None of these patients was seriously ill on admission, and all recovered.

The dosages of the antibiotics were:

Penicillin 2 mega units daily in three divided doses intramuscularly; streptomycin 2 g. daily in two or three doses intramuscularly (given in the same injection as penicillin); chloramphenicol 2 g. daily in four doses; tetracycline 3 g. daily in four doses; erythromycin 1·6 g. daily in four doses.

In a few seriously ill patients penicillin and streptomycin were given initially intravenously in doses of 250,000 units and 0·25 g. respectively. When erythromycin was used the first dose (250 mg.) was usually given intravenously. Streptomycin was stopped after seven days in most cases, penicillin being continued thereafter as a rule until radiographic clearing was maximal.

Corticosteroids

12 patients received treatment with corticosteroids. 2 were already receiving long-term prednisolone (1 with "honeycomb lungs" and 1 with diffuse interstitial pulmonary fibrosis), and the dosage was increased over the period of stress. In 2 patients prednisolone was given for relief of bronchospasm.

In the remaining 8 patients, who had fulminating or severe pneumonia, corticosteroids were used purely on an empirical basis—either prednisolone by mouth or hydrocortisone intravenously. Prednisolone was given in a dose of 40 mg. daily for three to five days and then reduced by 5 mg. per day, the drug being withdrawn entirely after eleven to fourteen days. 5 patients, who were initially unable to take prednisolone by mouth, received hydrocortisone 200 mg. intravenously daily. There was no obvious effect from this treatment in the 3 patients with fulminating staphylococcal infection, but as 2 of them died within twenty-four hours of receiving the first dose our assessment of its value might be misleading. Certainly it did not produce any dramatic benefit. In 2 young patients resolution of pneumonic consolidation was remarkably rapid, and in 2 others it pursued a normal course, but in the 5th patient the pneumonic consolidation progressively extended during the nine days she was receiving prednisolone along with full antibiotic cover. She died from anoxaemia uncontrollable by oxygen. Necropsy showed almost total bilateral consolidation. Histologically there was a remarkable lack of cellular reaction in the consolidated lungs: this may have been a consequence of corticosteroid therapy.

Other Treatment

36 patients needed oxygen therapy. 6 of the patients with severe pneumonia were treated in tents, and in the remainder oxygen was administered by a plastic 'Poly-mask' (British Oxygen Company). In only a few cases, all of them with advanced emphysema, was it found necessary to curtail the administration of oxygen because of carbon-dioxide retention. The usual [illegible] were almost invariably successful in relieving bronchospasm, and only 2 patients needed corticosteroids for this purpose. Pleuritic pain was treated with simple analgesics or pethidine, and chloral hydrate was the standard hypnotic. Opiates and barbiturates were strictly avoided because of the danger of their depressant effect upon the respiratory centre.

Special therapeutic measures were necessary for three important complications.

1. *Respiratory obstruction.*—In 9 of the 125 patients evidence of respiratory obstruction developed. 6 patients with laryngotracheitis had relatively mild obstructive features, and 3 patients with fulminating staphylococcal pneumonia had severe—indeed almost total—obstruction of the trachea and bronchi. The 6 mild cases all recovered without tracheostomy. 3 of them were treated in steam tents: [illegible] was used in some cases, but the steam did not appear to help them to cough up sputum more easily nor relieve the obstructive symptoms.

A tracheostomy was made in 2 of the 3 patients with severe respiratory obstruction, and there is no doubt that it saved life.

A woman, aged 23, was examined by bronchoscopy as soon as signs of respiratory obstruction were recognised. When the bronchoscope was passed between the vocal cords the [illegible] was seen to be almost totally occluded by [illegible]. It was felt that an attempt to remove this material by suction through a bronchoscope might be dangerous in this emergency. [illegible] to the patient's survival. The bronchoscope was [illegible] and a tracheostomy made immediately. [illegible] rubber tube. [illegible] recovery.

The 3rd patient [illegible]

2. [illegible]

this complication was controlled by oxygen therapy, nikethamide, and aminophylline until the acute infection began to resolve. In 2 cases, however, positive-pressure respiration with the Radcliffe apparatus was required to combat severe carbon-dioxide retention.

In the 1st case adequate pulmonary ventilation was maintained for three weeks, but evidence of grave respiratory insufficiency reappeared when attempts were made to wean him from the apparatus, and during one such attempt he died suddenly.

In the 2nd patient the respiratory insufficiency was less severe and it was hoped that positive-pressure respiration would not be required for more than a few days, but superinfection developed with *Staph. pyogenes* resistant to all antibiotics except erythromycin. This resulted in a rapid extension of pneumonic consolidation, and despite the administration of erythromycin he died.

4. *Peripheral circulatory failure.*—5 patients with this complication, which in each case was associated with severe anoxæmia, were treated with noradrenaline by intravenous drip infusion. 2 had fulminating staphylococcal lobular pneumonia, 2 had very extensive consolidation, and 1 had lobular pneumonia as well as respiratory insufficiency due to severe emphysema. In 1 patient the blood-pressure rose to normal and was maintained after the infusion was discontinued. By this time, however, the anoxæmia had also been substantially corrected. In 3 other patients there was only an initial response, and all died in peripheral circulatory failure with unrelieved anoxæmia. In the 5th case increasing doses of noradrenaline maintained the blood-pressure at normal levels for several hours, but the patient died.

Results

All the 14 patients in the laryngotracheitis group made an uneventful recovery in the course of a few days.

Of the 42 patients with bronchitis and bronchiolitis, 3 died.

1 patient with an acute exacerbation of chronic bronchitis died from congestive cardiac failure. 2 patients died with bronchiolitis: in the 1st, who had the Hamman-Rich type of diffuse pulmonary fibrosis, acute right ventricular failure developed, and in the 2nd, who was subject to chronic asthmatic bronchitis, the cause of death was a combination of staphylococcal bronchiolitis and respiratory insufficiency.

The remaining patients in this group all recovered completely, though convalescence was long in some with chronic bronchitis.

Of the 69 patients with pneumonia, 12 died.

4 had fulminating staphylococcal lobular pneumonia, and in 1 (already discussed) the major factor in the fatal outcome was respiratory obstruction caused by membranous mucosal sloughs in the trachea and bronchi. In none of the other 3 cases had there been any clinical evidence of respiratory obstruction, but in all of them necropsy showed, in addition to pneumonia, an acute inflammatory necrosis of the trachea and bronchi. In only 1 case was the classical picture seen of extensive hæmorrhagic consolidation and pulmonary œdema. Of the remaining 8 patients the cause of death was respiratory insufficiency in 1, massive pneumonia in 3, congestive cardiac failure in 3, and pulmonary infarction in 1. 5 of these 8 patients had a history of chronic respiratory disease. Of the other 3, 1 had mitral stenosis and was six months pregnant, 1 was obese, and the 3rd, who had been previously well, died as a result of massive pneumonia caused by cross-infection with *Staph. pyogenes* resistant to all antibiotics except erythromycin.

In 50 of the remaining patients clinical recovery was full and radiographic clearing complete. In 7 residual opacity, thought to be due to pulmonary fibrosis, persisted at the site of the pneumonia after a follow-up of at least six weeks. The causal organism in 5 of these patients was *Staph. pyogenes*. The only other complication, encountered in 5 cases, was postpneumonia serous effusion. Empyema did not develop in any.

Discussion

In the recent epidemic of Asian influenza in Great Britain the incidence of secondary staphylococcal infection has been high, and in this respect our series has been no exception. This high incidence had in our experience three important consequences: in the first place, several patients had a rapidly progressive illness of extreme severity, in the second, we had problems arising from drug resistance, and in the third, we had to act to reduce the risks of cross-infection with drug-resistant staphylococci in the hospital wards. These particular problems, though of great practical importance, concerned relatively few patients, but in future epidemics the therapeutic position may be less favourable—particularly if the newer antibiotics such as erythromycin have, as seems likely, been used in a needlessly extravagant manner during the past four months.

Clinical and Radiographic Features

Our clinical classification of the respiratory complications of influenza was devised before we consulted the reports of previous epidemics, and we were struck by its similarity to those adopted by Scadding (1937), Tyrrell (1952), and Stuart-Harris (1953). In the mildest cases it was very hard to prove secondary bacterial infection, and several of those classified under "laryngotracheitis" may have merely had a severe but uncomplicated virus infection. On the other hand the patients with respiratory obstruction in the laryngotracheitis group and those in the bronchitis/bronchiolitis group probably all had secondary bacterial infection, in some cases staphylococcal, and the prompt intensive treatment with antibiotics may have prevented the development of more serious complications in some. As expected, pre-existing chronic respiratory disease, notably bronchitis and emphysema, predisposed to respiratory complications, particularly in the bronchitis/bronchiolitis group, and lobular consolidation was commoner when there was a history of chronic respiratory disease, while lobar or segmental consolidation predominated in the others. Surprisingly, however, staphylococcal infection was less common in patients with a history of chronic respiratory disease than in others. Patients with *Staph. pyogenes* in the sputum who developed bronchiolitis or pneumonia were usually more seriously ill than those with other organisms. *Staph. pyogenes* was, moreover, isolated from all patients with fulminating illness. The clinical picture in these patients surpassed, in gravity and rapidity of progression, any type of pneumonia in our previous experience. In all 6 pulmonary consolidation was extensive, but in 3 this was of less immediate danger to the patient than coexisting respiratory obstruction caused by necrotising tracheobronchitis. 1 of these patients died from asphyxia, and the other 2 would certainly have died in the same way if the respiratory obstruction had not been relieved by bronchoscopy or tracheostomy at virtually the last moment. An obstructive lesion can readily be overlooked in these desperately ill patients, and death from asphyxia is not uncommon in fulminating staphylococcal infections before pneumonic consolidation has become dangerously extensive or toxæmia irreversibly profound.

Prognosis

In patients with fulminating staphylococcal infection the prognosis is probably related more closely to the virulence of the infection than to the treatment, but two points are evident:

1 Unrelieved respiratory obstruction is an important cause of death in these cases, and must be treated as a matter of supreme urgency

2 No time must be lost in starting effective antibacterial treatment, and for that reason the chemotherapy must be planned on the assumption that the causal organism may be resistant to one or more of the commoner antibiotics

The prognosis in other patients is generally favourable, but a few deaths are probably inevitable in elderly patients, particularly those with advanced emphysema In our series resolution of pneumonic consolidation was, on the whole, rapid and late complications were few

Bacteriological Features

In patients without *Staph pyogenes* in the sputum on admission the bacteriological findings did not differ significantly from those usual in bronchitis and pneumonia apart from an influenza epidemic, the pneumococcus and *H influenzæ* were the most important pathogens The sensitivity of those organisms to antibiotics followed the usual pattern, and the administration of an antibiotic to which the organism was sensitive was invariably followed by its elimination from the sputum and by clinical improvement

The position with *Staph pyogenes* infections was much more complex in that the organism was resistant to penicillin in more than 50% of cases and to at least one other antibiotic in some instances In only 1 case on admission, however, was the staphylococcus resistant to penicillin, streptomycin, tetracycline, and chloramphenicol, and resistance to erythromycin was not recorded In practice, the chief difficulty was to decide which antibiotic or combinations of antibiotics to use before the results of sensitivity tests became available

Our initial policy, of using a combination of three antibiotics, was intended to provide the best protection against the staphylococcus, short of giving erythromycin In fact this therapeutic regime proved dangerous since it sterilised the respiratory tract and in several cases allowed the establishment of an infection with staphylococci resistant to a wide range of antibiotics Most of the patients cross-infected with resistant staphylococci did not develop a recognisable clinical illness In 3 cases, however, cross-infection caused grave (in 2 cases fatal) consequences A tracheostomy had been made in 2 of these 3 patients, and we believe that this was important in facilitating cross-infection In none of the 3 cases was the organism resistant to erythromycin This drug was probably life-saving in 1 patient, but its administration was begun too late in the other 2

Tragedies of this kind are almost certainly avoidable if three precautionary measures are taken during epidemics of influenza,

1 Antibiotic therapy should be restricted at the earliest possible stage to an effective minimum to prevent the creation of an ecological vacuum which provides ideal conditions for cross-infection

2 All patients with a tracheostomy should be isolated and a strict "barrier-nursing" technique observed to minimise the danger of cross-infection Since we have adopted these measures there has, in fact, been no cross-infection in this type of case The same precautions should probably be taken in all patients with severe respiratory infection

3 All patients and staff in wards where respiratory complications of influenza are being treated should have nasal swabs examined bacteriologically every week, and the anterior nares of all persons harbouring coagulase-positive staphylococci should be treated with ointment containing chlorhexidine or neomycin and bacitracin All patients with sputum should have a specimen examined every week, and those from whom resistant staphylococci are cultured should be removed to an isolation block The object of these measures is of course to reduce as far as possible the reservoir of drug-resistant staphylococcal infection Nose swabs from 32 patients and staff shortly after the beginning of the epidemic yielded *Staph pyogenes* on culture in 13 cases (41%), the corresponding number for 57 patients and staff in mid-December was 34 (60%) The proportion of strains of *Staph pyogenes* resistant to antibiotics was much higher in the later group

The strict application of these three precautionary measures is of course extremely difficult, but in our opinion it must be attempted if further catastrophes of the kind we have described are to be avoided in future

Treatment

Chemotherapy —The ideal chemotherapeutic regime for the respiratory complications of influenza is one which, while disturbing the normal bacterial flora as little as possible, is able to control most types of secondary bacterial infection and to provide *reasonable* protection against the possibility of drug resistance if the secondary invader is a staphylococcus

It is our belief that these conditions are satisfied in cases of average severity by the combined administration of penicillin 2 mega units daily, and streptomycin 2 g daily This will control infection by pneumococci, hæmolytic streptococci, *H influenzæ*, and (at present) most strains of *Staph pyogenes* When the results of bacteriological examination, including sensitivity tests, are available, it will often be possible to stop the streptomycin, occasionally, when a staphylococcus is cultured, another drug will have to be substituted, in which case it is probably advisable to move the patient to an isolation block to prevent cross-infection During an influenza epidemic, when staphylococcal infection is common, the use of the wide-spectrum antibiotics should be kept to a minimum, both in post-influenzal respiratory illnesses and in infective exacerbations of chronic bronchitis and bronchiectasis The second group of cases is a particularly important source of staphylococcal cross-infection in hospital wards during influenza epidemics and, when influenza is rife, such patients should be admitted to hospital only for compelling reasons

Patients with fulminating illnesses should be treated initially with erythromycin 0 4 g six-hourly, in addition to penicillin and streptomycin, on the ground that if the infection is due to a staphylococcus resistant to penicillin or streptomycin this information may not become available until it is too late to save the patient's life with erythromycin It is, however, important that the administration of erythromycin be stopped as soon as the results of sensitivity tests show that it is no longer needed If a staphylococcus sensitive only to erythromycin is obtained, the patient must at once be transferred to an isolation block to continue treatment there

Tracheostomy now has an established place in the treatment of obstructive tracheo-bronchitis complicating influenza It may also be needed occasionally in patients with bronchiolitis or pneumonia who have serious and continued difficulty in raising sputum, and it is of particular value when these conditions complicate chronic bronchitis and emphysema Here positive-pressure respiration may occasionally be needed to tide the patient over a period of respiratory insufficiency

Bronchoscopy may be invaluable as an emergency measure for the relief of respiratory obstruction, whatever its cause, but frequent bronchoscopy is probably harmful, tracheostomy is preferable Bronchoscopy via a tracheostomy may be of considerable value in removing sloughs from the trachea during the week following tracheostomy for obstructive tracheo-bronchitis

Where severe asthma or adrenal insufficiency coexists it is rational to use *corticosteroids* Where the patient has been receiving corticosteroids for some other condition it is important to increase the dosage temporarily during the period of stress Their value in other cases is, however, doubtful Although it would be wrong to deny that these agents may have life-saving properties in fulminating infections, there is no convincing evidence that this is so Only a controlled clinical trial could provide this information At present corticosteroids have no established place in the routine treatment of the respiratory complications of influenza

Summary

125 patients with respiratory complications of influenza were admitted to three Edinburgh hospitals during six weeks in Autumn, 1957

Staph pyogenes was commonly found, especially in patients with pneumonia and in all with fulminating pneumonia

Respiratory obstruction developed in 9 patients, necessitating tracheostomy (which was life-saving) in 2

Similar cases in future should be treated by a combination of penicillin and streptomycin until bacteriological studies indicate a specific drug Bronchoscopy may be needed for respiratory obstruction, but tracheostomy is preferable to repeated bronchoscopy The value of corticosteroids remains uncertain Isolation of patients, where indicated, will reduce the risks of cross-infection

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ADULT SCURVY

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During the last ten years several authors have remarked on the rarity of adult scurvy Riches (1954) stated that "frank scurvy is now almost a clinical curiosity in this country" Hughes and MacLennan (1954) wrote of vitamin C "The gross *deficiency* which produces scurvy only occurs in exceptional circumstances" Isolated cases of scurvy are considered to be unusual enough to merit their publication (Barnes 1947, Mallam 1948, Roughton and Waldron 1951, Dewhurst 1954)

I report here 11 cases of adult scurvy and analyse the clinical picture seen in these cases The 11 patients were seen in 1951–57 in the wards and outpatient departments of two London teaching hospitals There were 10 males and 1 female, and their ages ranged from 48 to 82, with an average of about 65 Only 1 patient was married and living with his wife 4 were single males living alone, 3 were widowers living alone, and 3, including the 1 woman, were "separated" and living alone

A history suggestive of deficient vitamin-C intake was obtained in every case, and the dietary histories of the 11 patients can be divided into three groups

Fig 1—Small bruises of scurvy

Group 1 7 elderly men, each living alone For various reasons these patients had not looked after themselves properly, and their diets showed a curious uniformity, consisting almost entirely of tea, toast, bread-and-butter, and meat-paste or fish-paste sandwiches The duration of the diets in many of these patients was difficult to estimate, but in no case did it seem to have been less than six months

Group 2 2 men with duodenal ulceration and 1 woman alleged to have chronic cholecystitis All these patients, on medical advice, were taking a diet of fish, chicken, eggs, mashed potato, bread-and-butter, and milk drinks The woman had kept to her diet for four years, the 2 men to theirs for a year and for eighteen months

Group 3 consisted of only 1 man, who may justifiably be called a "food crank" He said he was a vegetarian, but his diet consisted solely of wholemeal bread, margarine, cheese, milk, honey, and eggs He had been living on this diet for many years

Only the woman and the "vegetarian" had active jobs Of the remaining 9 patients 6 were retired and 3 were out of work

Symptoms of Scurvy

Pain—8 of the 11 patients complained of an aching pain in the limbs, particularly the legs, and in the back Some of them described the pain as "rheumatic" The pain seemed to appear shortly before any obvious signs of bruising were noticed

Anorexia was present in 8 patients and often became more pronounced when the bruising appeared

Lethargy was described as a feeling of tiredness or of weakness or both 6 patients complained of it, and it was very striking in 2 of them, who found it difficult to get out of bed to feed themselves because of it

Other and less common symptoms—Stiffness of the legs was a prominent symptom in 6 of the 11 patients but was always related to the degree of swelling of the legs caused by extravasation of blood into the tissues Dyspnœa was noticed by 4 patients, but all four had a severe degree of anæmia 2 patients complained of a peculiar dry cough, and 1 of them had an aching pain in the chest 2 patients were admitted to hospital because they were found "collapsed" No reason other than scurvy was discovered to explain this

Signs of Scurvy

Bruising was the most characteristic feature There were two types

(1) Small spontaneous painless bruises 1–8 cm in diameter, scarcely raised above the level of the surrounding skin, and found most often on the hands, arms, and legs (fig 1)

(2) Extensive spontaneous extravasation of blood into the tissues, usually of the legs, causing purplish discoloration of

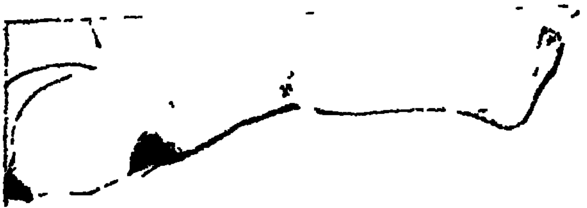

Fig 2—Large extravasation of scurvy

the skin, swelling and stiffness of the limb, and slight pain (fig 2)

All the patients had the small bruises, and 6 of the 11 had extravasation

Purpura —Hæmorrhages about the size of a pin's head into the skin were seen in 6 cases Bartley et al (1953) mentioned hæmorrhages surrounding the hair follicles as an early sign of deficiency, but only 2 examples of this lesion were seen in the present series 1 of the 6 patients with purpura had splinter hæmorrhages under the nails

Hyperkeratotic hair follicles were seen in 6 of the 11 patients It was most usually found on the outer aspects of the upper arms, on the thighs, and on the abdomen. This was one of the earliest lesions noticed in the experimental cases described by Bartley et al (1953), but in clinical cases its value as a diagnostic point is limited because similar lesions are often seen in patients without scurvy

Psychological effects —Little attention has been paid to this aspect of scurvy More than half the present patients on admission to hospital were depressed, resentful, and rather uncooperative After a few days' ascorbic-acid treatment, however, this state disappeared and the patients became normal and cheerful

Fever and jaundice —4 patients showed a slight tinge of jaundice when first seen, but this cleared rapidly and was thought to be due to the absorption of extravasated blood 3 patients had a low-grade irregular pyrexia, probably due to the effects of the bruises and the extravasation

Swollen spongy gums —The typical scorbutic lesions of the gums developed in only 1 patient and then to a very mild degree In 1 other patient a few small purpuric spots were seen on the gums and the gums bled more easily than usual when he brushed his teeth 7 of the 11 patients had no teeth This may have some bearing on the low incidence of bleeding spongy gums in the series, but of the 4 patients who had teeth 2 had healthy gums, the other 2 having the gum changes already described

Cases with an unusual history —1 patient came to hospital because he had had painless hæmaturia for five days and had passed a black, tarry stool Investigation of the urinary and gastro-intestinal tracts revealed nothing to explain the bleeding Because of the characteristic bruising seen on the skin he was treated with ascorbic acid and rapidly recovered Another patient had a large tender abdominal mass, which caused considerable diagnostic difficulty It was not for some days that the significance of the small bruises was realised but on ascorbic-acid therapy the mass, which was a retroperitoneal hæmatoma, gradually disappeared

Blood changes —Of the 11 patients 9 were anæmic, and in 6 of these the hæmoglobin was less than 55% 5 of the 9 anæmic patients had a normocytic normochromic type of anæmia, while 4 of them showed a macrocytic blood-picture There seemed to be no correlation between the severity of the anæmia and the degree of extravasation of blood into the tissues Bone-marrow examinations were carried out in 4 patients, 2 with macrocytic anæmia and 2 with normocytic anæmia, before any treatment had been given In all 4 cases the marrow showed normoblastic hyperplasia The white-cell count, platelet count, bleeding-time, and clotting-time were normal in all the patients Hess test for the production of petechial hæmorrhages was positive in 4 of 6 patients, but in 1 patient this test caused a large painful hæmatoma to appear in the muscles of the arm below the sphygmomanometer cuff

Vitamin-C saturation test —This test (Harris and Abbasy 1937) is not considered to be very reliable (*British Medical Journal* 1945, Bartley et al 1953), it was therefore done in only 4 cases 1 patient became "saturated" in seven days, and the remaining 3 were still "unsaturated" after nine days, when the tests were abandoned These results tend to confirm the diagnosis of scurvy in the 4 cases

Treatment

Ascorbic acid in doses of 600 mg a day was given to all the patients except those on whom a saturation test was done, when the dose was 700 mg a day 5 of the patients received a standard ward diet, ascorbic acid, and no other medication The remaining 6 patients were given ferrous sulphate and vitamin-B complex as well as ascorbic acid

Results

Of the 11 patients 9 felt a subjective improvement within twenty-four hours of the first dose of ascorbic acid, and in all the patients the lethargy, anorexia, and pain began to diminish in two or three days Within a week the purpura and smaller bruises had gone from the skin and the extravasation of blood into the limbs had begun to regress

Of the 5 patients who received only ascorbic acid 4 had reticulocyte counts done during the first ten days' treatment. The hæmoglobin levels of these 4 patients at the beginning of treatment were 53%, 52%, 49%, and 34%, and the reticulocytes increased from 2% or less to 10%, 9%, 6%, and 23% respectively In a month the hæmoglobin values in these patients had increased to 75%, 90%, 96%, and 92% respectively All the anæmic patients, whether on ascorbic acid alone or on vitamins B and C with iron, responded at much the same rate, and there seemed to be little difference between the two groups

Discussion

The clinical picture of scurvy seen in this series of cases differs in several respects from the descriptions found in current textbooks of medicine

The condition most often emphasised in textbook descriptions is that of swollen and bleeding gums Richardson (1956) states that "the first characteristic symptom is usually bleeding swollen gums ", and Whitby and Britton (1953), Davidson (1956), and Conybeare and Mann (1957) all emphasise the importance of this manifestation of scurvy In the present cases, however, only 1 of 11 patients showed evidence of swelling and bleeding gums It is not clear why this physical sign should be so strongly emphasised in current descriptions since some of the earlier writers were well aware of this pitfall Smith (1909) makes the following statement

> "The affection of the gums and the subcutaneous indurated swellings are the two especial lesions of scurvy The former, though generally regarded as a test symptom, is by no means constant."

McMillan and Inglis (1944) found bleeding gums in only 8 of 53 cases of scurvy (16%)

The commonest physical finding in the present series was of small spontaneous bruises on the limbs Although these are clearly not pathognomonic of scurvy they form an important early indication that the diagnosis of scurvy should be considered, a fact which receives little attention in many of the textbooks Some current descriptions refer to tender lumps and indurated swellings which are seen in severe scurvy and which occurred on 3 occasions in the present series a retroperitoneal hæmatoma, a spontaneous hæmatoma on the buttock, and a hæmatoma which appeared in the arm as a result of Hess' test The type of extravasation shown in fig 2 and seen in 6 patients, however, is rarely mentioned

There appear to be differences between cases of scurvy induced experimentally (Bartley et al 1953) and those seen in clinical practice Perifollicular hæmorrhages, an early sign in the experimental cases, were seen in only 2 of the present patients The acneiform lesions described in the experimental series were not seen in the clinical cases, but perhaps the difference in age between the two groups might have some bearing on this point, because the ages of the experimental group ranged from 21 to 34, whereas the clinical group had an average age of 65

In the present series, anæmia was common and important In the experimental cases (Bartley et al 1953), however, anæmia did not develop, indeed it was questioned whether there was such an entity as an anæmia due to pure deficiency of vitamin C Bronte-Stewart (1953), working in South Africa, found that anæmia was common in his cases of scurvy and that prompt hæmatological response followed the administration of pure ascorbic acid alone Barnes (1947) suggested that the degree of anæmia in scurvy was related to the amount of blood lost by extravasation This was not confirmed by Bronte-Stewart's (1953) investigations, nor is there any correlation between the degree of anæmia and the extent of the extravasation in the present cases It seems likely that the degree of anæmia is related to the severity of the scurvy and to the length of time during which the patient has not been taking enough vitamin C In the experimental cases (Bartley et al 1953) the experiments were terminated before any of the subjects developed signs of severe scurvy, this may explain the absence of anæmia In clinical cases it is difficult to judge the duration of the vitamin deficiency, but it may well be months or even years in many cases That anæmia often develops in scurvy and quickly responds to pure ascorbic acid, however, is confirmed

Summary

11 patients with scurvy are discussed, each of whom was living on a diet deficient in vitamin C The cases fell into three groups elderly men living alone, those dieting because of medical advice, and the "*food crank*"

The chief symptoms were pain, lethargy, anorexia, and mental depression

The chief signs were small bruises on the limbs, extravasation of blood into the tissues, and anæmia

Typical scorbutic lesions of the gums were seen in only 1 patient, but only 4 patients had any teeth

The symptoms and signs, including anæmia, responded promptly to ascorbic acid

Current descriptions of clinical and of experimental scurvy are contrasted with the present findings

My thanks are due to Sir Daniel Davies, Dr Frances Gardner, Mr H Daintree Johnson, Dr Una Ledingham, and Sir Cecil Wakeley for permission to publish, and to Dr R S Bruce Pearson for reading the manuscript

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AN ILLNESS RESEMBLING ACUTE POLIOMYELITIS

CAUSED BY A VIRUS OF THE RUSSIAN SPRING SUMMER ENCEPHALITIS/LOUPING ILL GROUP IN NORTHERN IRELAND

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LOUPING ill, which is transmitted by the tick *Ixodes reduvius* (Linn)[*] has been known to occur among sheep in Scotland and the north of England for more than a century (van Rooyen and Rhodes 1948) and is also present in Northern Ireland, particularly in the northern districts such as the Antrim glens and the Sperrin mountains (Prof H G Lamont, personal communication) The virus causing louping ill is so closely related to the virus of Russian spring-summer encephalitis (R S S E) that both may be considered to be strains of a single virus (Pond et al 1953, Pond and Russ 1955)

R S S E virus has been responsible for outbreaks of aseptic meningitis and encephalomyelitis in mid-European countries (Richling 1955, Kmet et al 1955, Moritsch and Krausler 1957) One of the most interesting features of R S S E was that in its spinal paralytic form it was often clinically indistinguishable from acute paralytic poliomyelitis It is perhaps surprising that in Great Britain and Northern Ireland only four naturally occurring cases of louping ill have been described in man (Davison et al 1948, Brewis et al 1949, Lawson et al 1949) These were cases of encephalitis in persons working with sheep

During 1957 we attempted to recover virus from the fæces in every case of poliomyelitis, aseptic meningitis, and encephalitis reported in Northern Ireland In a few cases diagnosed clinically as paralytic poliomyelitis virus was not isolated from the fæces, and serum-neutralisation tests did not suggest a recent poliovirus infection Because of the reported similarity of some European cases of R S S E to paralytic poliomyelitis we decided to test the serum of these patients for antibodies to the R S S E group of viruses Later, serum was tested from nearly all the patients diagnosed as having either paralytic poliomyelitis, aseptic meningitis, or encephalitis but from whose fæces no virus had been recovered Serological evidence of recent infection with a virus of the R S S E group was obtained in five cases, of which four had been diagnosed as acute poliomyelitis and one as mild encephalitis Of the four patients diagnosed as having acute poliomyelitis one had severe paralysis of a lower-motor-neurone type and the remaining three had mild paralysis

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[*] Synonym *Ixodes ricinus*

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Methods

Complement-fixation Test

Sera were stored at −20°C and inactivated for 30 minutes at 56 C before use Anticomplementary sera were treated first with equal amounts of undiluted complement and then inactivated for ten minutes at 62 C before use. After this treatment very few sera had to be discarded because of anticomplementary activity.

Hyperimmune serum was prepared in guineapigs by repeated intramuscular injections of a 20% suspension of mouse brain from paralysed mice infected with R.S.S.E virus

The antigen was prepared, according to the technique of Casals (1949), from infected mouse brain by repeated extraction of lipid materials with acetone and ether and final extraction with physiological saline solution at 4 C The strain of virus used was isolated from a fatal case of R.S.S.E in Slovenia in 1954, it had been found indistinguishable from the OM 64 strain obtained from Dr V Bardoš of Bratislava

A control antigen was prepared in the same way from healthy mouse brains

The test was made in plastic hæmagglutination plates with 0 1 ml volumes and 2½ minimal hæmolytic doses of complement

Serum, antigen, and complement were incubated overnight at 4 C, and then 0 2 ml of a suspension of sensitised sheep red blood-cells was added. The plates were placed at 37 C for 30 minutes after the addition of the hæmolytic system Cups showing 75% or more fixation were considered positive

Neutralisation Tests

These were made in mice aged 3 or 4 weeks Equal amounts of undiluted serum were mixed with both 10 and 100 mouse LD doses of virus and allowed to stand for an hour at room temperature and then for two hours at 4°C before inoculation. Each of the mixtures was inoculated intracerebrally in 0 03 ml amounts into four mice Controls were set up with each test. The mice were observed for ten days after the last control animal, which received virus alone, was dead

Sera which showed neutralisation of 10 or 100 LD_{50} of virus were tested with various dilutions of the virus from 10^{-3} to 10^{-7} by the same technique as described above to determine the neutralisation index

Results

Complement-fixation Tests

Three groups of sera were tested. The first group consisted of paired sera from 34 patients who had been diagnosed clinically as having had either paralytic poliomyelitis or aseptic meningitis but from whom no fæcal virus was isolated Four of these patients showed an increase of complement-fixing antibody in their convalescent serum In addition a single late convalescent serum from one patient with mild encephalitis was tested. The results of these tests are given in the accompanying table

Case no.	Age (yr)	Day of illness when serum was taken	Titre of complement-fixing antibody	Neutralisation index
1	23	9	<1 in 1	<10
		63	1 in 8	1000
2	21	5	<1 in 1	<10
		62	1 in 16	1000
3	42	3	<1 in 1	<10
		[illegible]	1 in 6	100
4	24	[illegible]	<1 in 1	<10
		[illegible]	1 in 4	300
5	21	62	1 in 8	50

The second group consisted of paired sera from 100 poliomyelitis patients in whom the diagnosis had been confirmed by isolation of the virus The first specimen of serum was taken during the first week of illness, and the second specimen about 20 days later Most of the patients were young children under the age of 5 years No complement-fixing antibodies for the R S S.E./louping ill group of viruses were detected.

The third group consisted of 66 paired sera collected from influenza patients in the late-autumn epidemic of 1957 Most of the patients were young adults In four cases antibodies to R.S.S.E. virus were found in both acute and convalescent sera at titres of 1 2

Neutralisation Tests

Acute and convalescent sera from the thirty-five patients of the first group mentioned above (all but one of whom had been clinically diagnosed as having poliomyelitis) were tested for neutralising antibodies Only those patients who had complement-fixing antibody were found to have neutralising antibody The neutralisation indices for these patients are given in the table.

Neutralisation tests were also done with the sera of the four influenza patients who had low-titre complement-fixing antibody None had neutralising antibody

Clinical Histories of Patients

The clinical histories (kindly supplied by their physicians) and symptoms of the five patients with serological evidence of infection with the R.S.S E /louping ill group of viruses are given below

Case 1—A man, aged 23, took part in an athletic meeting on Aug 8 and next morning felt extremely ill with pains all over and weakness in his arms and legs He also had headache and photophobia, and vomited three times during the afternoon. He had quite severe persistent pain around his left subcostal margin On examination after admission to hospital he had no pyrexia and all his reflexes were strong and equal on both sides Lumbar puncture on the third day of illness produced a clear and colourless fluid with protein 55 mg per 100 ml and no cells During the next day or two he developed a "dead feeling" and weakness in his right hand, and his back felt curiously weak and stiff His abdominal reflexes disappeared, and his right triceps jerk was slightly reduced He still had no pyrexia, and the muscular tenderness in his abdomen was diminishing On the seventh day he felt weak and "sweaty" while attempting to use an electric razor and complained that his arms felt very heavy He also felt sick, and his headache returned. In the next few days all his symptoms gradually disappeared, and by the eleventh day he had only slight weakness of his right thumb He made a complete recovery, but his abdominal reflexes were still absent after a month. He had been confined to bed for six weeks

Case 2.—A man aged 21, had an influenza-like illness in which he noticed weakness of his arms and felt pains in his legs. On the fifth day of his illness, when he was admitted to hospital, he could walk, but during the next few days severe paralysis of lower-motor-neurone type developed in both his arms and his legs He remained in hospital for three months and when seen a month later had recovered completely Though he lived in a town he often went for walks in fields where sheep grazed and in areas where ticks are said to be found. On admission to hospital he was infested in the inguinal region with what were thought to be *Phthirus pubis*, which were dealt with without being identified Possibly they were larvæ of the tick *Ixodes ricinus*

Case 3—A married woman, aged 42, became ill with pyrexia, headache, and vomiting After twenty-four hours she was admitted to hospital with neck stiffness, a positive Kernig sign, and slight weakness in her left arm and her left leg Her cerebrospinal fluid contained 250 cells per c.mm (polymorphs 70%, lymphocytes 30 %) Her neck stiffness remained for a few days, but the Kernig sign was negative on the second day after admission In a few days the weakness in both limbs disappeared.

Case 4—A married woman aged 24, became ill with general malaise and attacks of shivering a month after having a baby Because her symptoms persisted she saw a doctor after two days She then complained of sore legs and arms and profuse sweating during the night with vomiting and severe headache The doctor could find no signs indicating puerperal sepsis On admission to hospital stiffness of her neck and weakness of her four limbs were noted Her abdominal reflexes were absent on both sides She had pyrexia, which settled slowly by lysis in the next seventeen days A general improvement in her condition had been noted during the first week, and she had completely recovered when seen four months later

Case 5 —A male medical student, aged 21, became ill with acute headache, general weakness, and severe lumbar pain These symptoms lasted for a few days and then disappeared During this time the patient had a temperature of 101°F and vomited twice After apparent improvement and an interval of six days he developed a severe headache, and his temperature rose to 103°F The pyrexia was not constant, rising in the afternoon and falling to 99°F in the morning This second pyrexial stage lasted for six days, and the patient was then admitted to hospital but recovered completely after a short stay Five days before the onset of his illness he removed a tick from his arm and had kept it This was subsequently identified as an adult female *Ixodes reduvius*

There was no evidence that any of these five patients were infected at the same time or the same place Two came from Co Antrim, two from Co Londonderry, and one from Co Fermanagh

Discussion

It is usually considered that the clinical diagnosis of paralytic poliomyelitis in the British Isles is relatively easy It now appears that, in Northern Ireland at least, an infection with a virus of the R S S E /louping ill group must sometimes be considered as an alternative diagnosis The cases which we have described were discovered because an attempt was made to confirm the diagnosis in the laboratory of every case of paralytic poliomyelitis With the exception of the case of encephalitis the other four infections with R S S E virus clinically resembled acute poliomyelitis According to Grinschgl (1955) the clinical differential diagnosis is practically impossible in some cases It seems to us that the laboratory diagnosis of infection with R S S E virus will be important in the future in the assessment of paralytic infections in people who have received Salk-type poliomyelitis vaccine

The R S S E /louping ill group of viruses are transmitted among sheep by *Ixodes reduvius* (MacLeod and Gordon 1932) Transmission to man is also in some cases by ticks, but other arthropods may be responsible (Richling 1955) Of considerable interest are the observations that, in other cases, milk may play a part in the transmission of the disease to man (Moritsch and Krausler 1957, Dr V Bárdoš personal communication)

In only case 5 was there a definite history of a tick bite before the onset of illness The way in which the four other patients became infected is unknown Now that human infections are known to occur in Northern Ireland, the laboratory diagnosis is likely to be more prompt and should provide opportunities for studying the natural history of the disease

Summary

Five cases of human infection with a virus of the Russian spring-summer encephalitis/louping ill group in Northern Ireland are described

In four a provisional clinical diagnosis of acute poliomyelitis had been made

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MANUAL COMPRESSION OF THE CHEST AS AN AID TO DEMONSTRATING ADVENTITIOUS RESPIRATORY SOUNDS

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THOUGH radiology now has pride of place in the investigation of respiratory diseases, diagnosis in those disorders that do not cast shadows remains essentially clinical They are mostly disorders of the respiratory conducting system —tracheobronchitis, chronic bronchitis, and bronchial asthma—which cannot be recognised radiographically until secondary pulmonary changes develop Respiratory-function studies are also of little value in detecting the lesser degrees of impairment, for despite refinements, the persistently wide range of normal means that only conspicuous defects are significant (Woolf 1956)

In the patient complaining of dyspnœa due to obstructive bronchial disease, physical findings consist mainly of abnormal bronchial sounds Sought with the stethoscope their presence is usually confirmed with ease In early cases, however, abnormal sounds may not be elicited by standard procedures, and to assist in the examination of this type of patient I have used a simple physical manœuvre which often makes them audible through the patient's open mouth

Rales audible at the mouth were first described by the Swiss clinician Hermann Sahli In his writings at the turn of the century, he called them “ oral rales ” and considered them of diagnostic value, occasionally present when none could be heard at the surface of the thorax It was the production of these oral rales by manual compression of the chest that led to the observations I record here

The Method

The method is most effective if the patient strips to the waist and sits upright, preferably on a stool or forward from the back of a chair He is told to breathe slowly and as deeply as possible through his open mouth while the examiner, arranged to one side, cocks an ear beside the patient's mouth and places the flat surfaces of his hands on the anterior and posterior chest wall so that they lie opposed and separated by intervening lung Just before the end of expiration, the hands should be approximated in a sharp compressing movement that expresses a burst of residual air from the underlying tissues

In this way various areas of a lung field may be explored by selective compression in a methodical apex-to-base manœuvre, and the resulting sounds auscultated at the open mouth The only practical difficulties encountered thus far have been potentially confusing nasal whistles in persistent nose-breathers and the accidental expulsion of some loose-fitting upper dentures The former difficulty has been resolved by pinching off the nose, and the latter by removal beforehand

The Sounds Produced

Sounds produced in this way are essentially the same as those heard during standard auscultation, the trachea and bronchi serving in effect as an inverted stethoscope rooted in the depths of the pulmonary bed The soft bronchovesicular breath sounds of the normal lung are somewhat sharper at the mouth, approaching bronchial breathing in character but otherwise recognisable Rales (moist bubbling interrupted sounds) are easily recognised, while rhonchi (high-pitched continuous dry sounds) tend to be finer and sharper in pitch than when damped by transmission through the chest wall

Clinical Observations

Chronic Bronchitis

In a proportion of patients suspected of chronic bronchitis no abnormal physical signs could be detected by ordinary auscultation, but fine expiratory high-pitched wheezing rhonchi, quite distinct from the normal bronchovesicular sounds, were produced by the compression manœuvre The site of production varied from patient to patient

Bronchospasm

Episodes of respiratory difficulty sufficient to bring the patient for advice, yet insufficient to produce audible wheezes either at the time of the attack or at the time of auscultation, are not uncommonly observed in allergic states and in early chronic bronchitics during damp or humid weather Scattered fine rhonchi can almost always be demonstrated by manual compression of the chest

Chronic Left Ventricular Failure

Patients in this category complained of dyspnœa and fatigue aggravated by effort Associated cardiovascular findings included angina of effort, orthopnœa, ankle œdema, left ventricular enlargement, or electrocardiographic abnormalities

Any history of chronic productive cough or of susceptibility to " chest colds " in the winter rendered them ineligible for inclusion in this group of cases regarded as pure left ventricular failure On standard auscultation, a high proportion had persistent inspiratory crepitant rales—of the kind that can be imitated by rolling hairs between the fingers near the ear—over one or both lung bases Rales of this description could *not* be rendered audible by the compression manœuvre

Bronchial Stridor

In the single case of bronchial stridor (due to bronchogenic carcinoma) in which the manœuvre was performed there was no difficulty in discovering the side and lobe involved This experience suggests the use of the method in cases of aspirated foreign body, to facilitate bronchoscopy

Discussion

The normal exchange of respiratory gases is an almost silent process accompanied only by the soft rustling sounds of bronchovesicular breathing Normal bronchial lumina are clean windswept tunnels, untrammelled by collections of secretion, and the normal contraction during expiration of their smooth muscle, though shortening and narrowing them, does not do so to the extent of producing rhonchi (Best and Taylor 1945)

Adventitious chest sounds are the result of respiratory gas turbulence induced by irregularities in the lumen of the conducting vessel in addition to the direct action of air currents on the contained secretions For sounds characteristic of certain diseases to be audible on auscultation, respiratory gases must flow through the abnormal area at speeds sufficient to induce turbulence or vibration

A proportion of patients with respiratory disease fail to fulfil these criteria Some cannot achieve more than a gesture at maximal breathing, emptying no more than a quarter of their total alveolar capacity Others, as a result of obesity, advanced emphysema, or abdominal muscle weakness, lack a capacity for sharp expulsive effort and have a speed of emptying below that necessary to induce adventitious sounds

In health, alveolar ventilation is unequal despite free bronchial communication (Best and Taylor 1945) owing partly to the greater part taken in gaseous exchange by those alveoli nearest to the mobile surfaces of the thoracic cavity Is it not likely that, then, when a proportion of bronchioles are not freely patent, neighbouring alveoli expand to undertake gaseous exchange, and the normal expiratory pressure, which would have emptied the affected alveoli in health, is spent in emptying neighbouring alveoli through normal bronchioles? As a result, when uniform expiratory pressure is applied to areas of varying resistance (obstructed and unobstructed alveoli), those offering least resistance will empty most freely and dissipate the force, so preventing gases from the obstructed alveoli from passing quickly enough through the stenosed bronchioles to create adventitious sounds or to empty the alveoli adequately before the next inspiration If an inevitable volume of residual air must exist which the most vigorous expiratory efforts cannot dislodge, will it not tend to collect behind the relatively stenotic bronchioles beyond reach of the deepest respirations? Manual compression at the end of expiration should in theory encroach on this residual air, which occupies at least a quarter of the total alveolar volume, and use it to demonstrate the state of the lumina of its supplying bronchioles

In patients with a history suggestive of chronic bronchitis or mild episodes of bronchospasm, and in whom no adventitious chest sounds are audible on ordinary auscultation, the compression manœuvre often produces a rustle of hissing expiratory sounds within which extremely fine rhonchi can be discerned, quite distinct from normal bronchovesicular breathing Less often, isolated rhonchi alone can be demonstrated

In patients with early chronic left ventricular failure, persistent inspiratory crepitations at the lung bases have traditionally been considered evidence of pulmonary œdema Wood (1956), however, says they are often absent when failure exists, and when present are often due to chronic bronchitis, adding that crepitations due to pulmonary œdema are widespread in distribution rather than basal Sahli (Potter 1911) maintained that inspiratory basal crepitations are characteristic of left ventricular failure and result from a tearing apart of the engorged and approximated alveolar walls by the inspiratory air-stream If he was right, compression of crepitant lung bases due to early left ventricular failure should produce no audible oral rales—unless, of course, the œdema is advanced and involves the lumina of the larger bronchioles or there is associated bronchial disease This has been my own finding

Summary

This is a study of the value of a simple physical manœuvre of manual compression of the chest in eliciting adventitious pulmonary sounds

Lesser degrees of bronchial disease sufficient to provoke complaints of breathlessness but insufficient to produce signs by standard examination have usually been found to yield evidence on applying the manœuvre

Basal crepitations due to early pulmonary œdema are not heard on application of compression—a fact which

helps in distinguishing the crepitations of left ventricular failure from those of bronchial exudate

My thanks are due to Dr John Lewis, chief of service, medicine, and Dr N J England, chest physician, both of Westminster Hospital, London, Ontario, Canada, for valuable suggestions and criticism

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ANÆSTHESIA IN MASS EMERGENCIES

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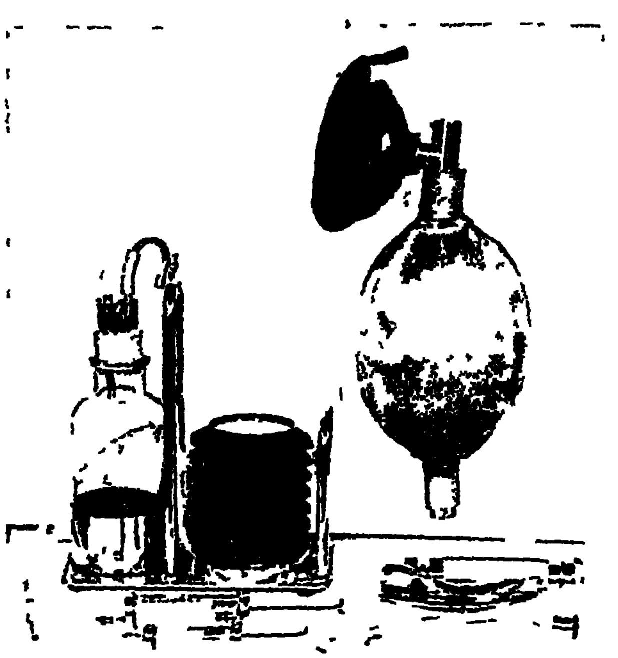
In civil and military emergencies, where many urgent operations will have to be done in a short time, the usual methods of anæsthesia may not be applicable

For instance, anæsthetic machines, such as are usual in operating-theatres and depend for their function on gas in cylinders, may not be available, and the supply of gases may have been destroyed—e g, by bombing and by fire—or difficulties of transport may render the supply uncertain or impossible In such a case one might expect to be able to fall back on the use of liquid anæsthetics (ether, chloroform) combined with atmospheric air as the source of oxygen (McAuley 1943), but even these may be unavailable, as in Hungary in 1956 (O Lippman, personal communication) Other forms of anæsthesia than inhalation—e g, local and intravenous anæsthesia (Dripps 1956)—would have to be used



Apparatus for anæsthesia and intermittent positive-pressure artificial respiration using atmospheric air

Since the equipment and the technique of intravenous administration of anæsthetics are extremely simple, its advantages are obvious On the other hand, the elimination of these drugs from the body depends on relatively slow detoxication, which involves a risk of overdosage caused by accumulation Moreover, the anæsthetist has to control the air-ways and maintain the efficiency of the respiratory volume No doubt, neglect of these factors, in addition to toxic lesions, contributed essentially to the high mortality connected with the use of barbiturates at Pearl Harbour in 1941 , Further, thoracotomy requires artificial respiration by intermittent positive pressure

In a previous paper a new apparatus was described (Ruben and Ruben 1957) which enables artificial respiration by intermittent positive pressure to be given with atmospheric air instead of gases from a cylinder The apparatus looks and is handled like the bag-and-mask commonly used by anæsthetists (see figure) This result has been reached by making the bag self-expanding With this device it is possible in practice to ensure sufficient ventilation for many hours

Method of Anæsthesia

To test the possibilities offered by anæsthesia for major surgery based exclusively on intravenous drugs, a series of anæsthetics were administered with the bag-respirator as the only apparatus

The purpose of the anæsthesia, apart from providing good conditions for operating, was to prevent deleterious effects of the operation on the circulation and to keep the patient " asleep " or, rather, to provide amnesia for the operation

Apart from premedication with pentobarbitone, morphine, and scopolamine, the only drugs used were thiopentone, pethidine, and *d*-tubocurarine chloride In addition the patients were given atropine and neostigmine at the end of the anæsthesia All the patients were intubated endotracheally, and during maintenance the tube was kept connected directly with the bag-respirator All the patients had controlled respiration throughout the operation

In addition to syringes, needles, and the bag-respirator, the anæsthetic equipment included a suction apparatus (Ruben and Ruben 1957), functioning independently of pressure-cylinder gas This device consists of a concertina bag and a trap bottle with tubes The suction, which is obtained by intermittently compressing the bag with the foot, is established by expansion of the concertina bag by the action of a spring

The patients were controlled during anæsthesia in the usual way—i e, by frequently recording the arterial blood-pressure and the pulse-rate and, in more than half the cases, by continuous electrocardiography recorded on an oscillograph In a few patients the oxygen content of the expired air was examined, and in some the volume of the air-exchange was checked on a gas-meter

For the patients' ages, operations, duration of anæsthesia, and quantities of anæsthetics given see tables I–VI

Comments

As might be expected, rather large quantities of thiopentone had to be used, especially at the beginning of an operation The actual quantity, of course, depended on the physical state of the patient, the duration of anæsthesia, and the kind of operation

By the method used it was difficult to determine the " depth of anæsthesia " due to thiopentone, the more so because relaxants had been used To estimate the central depression, the size of the pupils and the light-reflexes served as a guide Where the relaxation was not profound, slight movements of the fingers or toes served as a guide to the need of supplementary injections

TABLE I—AGE-DISTRIBUTION

Age (yr)	No of patients	Age (yr)	No of patients
9	1	40–49	11
10–19	6	50–59	14
20–29	1	60–69	10
30–39	11	70–76	4

Five patients had recollections of the operation Three of these did not remember having felt pain, but two, who remembered having suffered pain, found at least part of the operation disagreeable In all other cases there was total amnesia for the operation, and all the patients, apart from the two who had felt pain, found the anæsthesia satisfactory

TABLE II—OPERATIONS

Type of operation	No of operations
On the head	10
Transthoracic	5
Upper laparotomies	7
Lower laparotomies	6
Other operations	30

The anæsthesia was found fully satisfactory for securing good operating conditions When the patients were sufficiently awake to respond adequately when addressed, had satisfactory coughing and swallowing reflexes and a normal respiration, and were able to keep the air-ways free unaided, they were carried back to the wards This was possible 5-10 minutes after the end of the operation Especially after prolonged anæsthesia, however, the patients were rather sleepy, and, left alone, would fall asleep again, not being able to keep fully awake till several hours later

TABLE III—DURATION OF OPERATIONS

Duration (min)	No
25–59	9
60–119	19
120–179	12
180–239	10
240–299	2
300–359	2
360–560	4

A man, aged 69, who had undergone total gastrectomy for cancer of the stomach (duration of anæsthesia $6^{3}/_{4}$ hours) did not respond adequately until about sixteen hours after the operation During this time he was kept intubated and watched in the same way as patients recovering from anæsthesia After he awoke there were no other complications This case, one of the earliest in this series, was fully explained by overdosage of thiopentone

In five cases the technique described was used for transthoracic operations It was verified by analyses of arterial blood, that, during transthoracic operations, a satisfactory oxygen saturation of the arterial blood could be maintained even by breathing atmospheric oxygen, but in that case hyperventilation was necessary When the operation was finished and the patient was induced to breathe spontaneously, temporary hypoventilation was not allowed, because the use of atmospheric air alone made it impossible to compensate for a hypoxia produced by hypoventilation by increasing the oxygen content of the inspired air The supervision required by patients after this form of anæsthesia was similar to that necessary after ether anæsthesia.

TABLE IV—AMOUNTS OF THIOPENTONE USED

Thiopent. (mg)	No of operations
250–475	7
500–975	30
1000–1475	12
1500–1975	6
2000–2150	3

TABLE V—AMOUNTS OF PETHIDINE USED

Pethidine (mg)	No of operations
0	2
10–45	21
50–95	27
100–125	6
185	1
340	1

Conclusion and Summary

With the drugs and bag-respirator in question satisfactory anæsthesia was induced and maintained for numerous operations The technique is extremely simple in the hands of an experienced anæsthetist and, in emergencies, allows a large number of patients to be anæsthetised On the other hand, it needs experience to avoid overdosage and insufficient amnesia Ether and air, administered on an open mask or with a vaporiser, or used with an ordinary anæsthesia machine, is undoubtedly less dangerous in the hands of people with little training

TABLE VI—AMOUNTS OF TUBOCURARINE USED

d-tubocurarine chloride (mg)	No of operations
15–29	11
30–49	19
50–69	16
70–90	10
115	1
133	1

Provided the anæsthetist has the necessary technical training, this method enables anæsthesia to be induced and maintained with simple means for transthoracic operations and operations on the head, even under the most primitive conditions

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" Tobacco-smoking, a few years ago, was carried in this country to a great excess, and now, according to the statistical returns, the annual consumption of tobacco is very large It is, however, no longer a *fashionable* habit in our streets, and the prohibitions which exist against its use in various places of public resort, may eventually have the effect of still further diminishing the pernicious custom "—*London med Gaz* 1845, 38, 236

Preliminary Communication

HYPOPHYSECTOMY COMBINED WITH INTRASELLAR IRRADIATION WITH YTTRIUM-90

HYPOPHYSECTOMY causes improvement, which can be assessed objectively, in about half to two-thirds of patients with advanced mammary cancer[1-5] Irradiation of the pituitary gland with radon seeds or with ^{90}Y (a pure β-particle emitter) causes improvement in about a third to a half of the patients[6 7] There is little agreement about the choice of patients likely to benefit from these therapeutic measures

One of the problems is to ensure that all the glandular tissue is either removed or destroyed Falconer[3] reported that 1–10% of the gland was still present after hypophysectomy (plus treatment of the fossa with Zenker's fluid) in 6 patients at necropsy, and Olivecrona[1] found that removal was incomplete in many of his cases Forrest[6] found that irradiation with radon did not produce complete necrosis in any case examined post mortem, and that ^{90}Y caused complete destruction in only 2 cases out of 7 Our own experience with surgical hypophysectomy and with radon has been similar

For these reasons we have tried to destroy the gland completely by combining surgical hypophysectomy with subsequent irradiation of the pituitary fossa After some trial and error we have evolved the following method

TECHNIQUE

Surgical hypophysectomy is done by the right transfrontal route When as much gland as possible has been removed and hæmostasis secured, the fossa is packed with yttrium-90 oxide (7 5-10 0 mC) mixed with dental impression wax

The radioactive material is prepared in the following way at the isotope division of the Atomic Energy Research Establishment, Harwell the irradiated yttrium-oxide powder is added to about 1 ml of molten wax, the mixture is agitated to ensure a uniform distribution of the powder and cooled rapidly to prevent sedimentation

The wax is flown to Belfast in time for the operation On arrival the pellet is rolled between two thick flat pieces of 'Perspex' into a long cylinder and loaded into a piece of glass tubing, 30 0 cm long and 0 5 cm in internal diameter, which has been lubricated with liquid paraffin A metal plunger (with a flat, not a rounded, end) is inserted at one end, and the "syringe" thus formed is taken, enclosed in a perspex case, into the operating-theatre

The procedure is carried out aseptically, and strict precautions are taken against contamination of apparatus and personnel with radioactive material The operator places the end of the "syringe" in the fossa and extrudes the radioactive wax by depressing the metal plunger The wax emerges in a worm-like form and moulds itself roughly into the shape of the fossa Finally it is packed in tightly with a long-handled spatula and covered with a small piece of muscle and some fibrin foam to protect the overlying structures

All concerned with the radioactive material wear thick perspex shields over their eyes while handling it The contaminated instruments are stored until they become inactive Cortisone is given from two days before the operation, and thyroid extract from about a month after

RESULTS

Clinical

25 operations were done between May and November, 1957 5 patients died postoperatively. 4 of these were aged more than 60, and 3 had severe pulmonary involvement preoperatively Of the 20 who survived operation 16 (80%) have shown objective evidence of remission (see table) All but one of those who had blood-borne metastases improved (94%), and none of those with local disease only showed any sign of remission Only 1 patient has had recurrence of disease after an initial remission, she died from cerebral metastasis six months after the operation Complications included major damage to the optic nerves in 2 patients

CLINICAL RESULTS OF HYPOPHYSECTOMY AND IRRADIATION OF PITUITARY FOSSA IN 20 PATIENTS SURVIVING OPERATION

Extent of disease	No surviving operation	No undergoing remission initially
Local disease only (breast, chest wall, and adjacent lymph glands)	3	0
Blood-borne metastases with or without local disease	17	16 (94%)
Total	20	16 (80%)

One had blindness in one eye and a temporal-field defect in the other as a result of irradiation She had a pre-fixed chiasma and a small slit-like fossa As a result no protective covering could be placed over the wax She showed general improvement, however, and regarded the operation as well worth while

The other developed complete bitemporal hemianopia following operative trauma

4 patients developed contralateral 3rd-nerve lesions, due probably to forcing the wax through the lateral wall of the fossa We have learnt to avoid this complication All the patients have developed diabetes insipidus and require intramuscular pitressin tannate (1 ml of an oily solution containing 5 pressor units) every two days

Endocrinological Assessment of Pituitary Function

Thyroid function was assessed preoperatively in all the patients and a month postoperatively in those who were well enough (17) The neck uptake fell below 10% and the T index of urinary excretion[8] fell to a myxœdematous level (below 2 8) in all

Gonadotrophins were estimated in the urine at the same time by the method of Butt[9] A month after the operation they were absent in 8 of 9 patients in whom the results are available

The vaginal cytology was examined similarly 18 showed evidence of œstrogen activity before operation, and only 1 of 19 a month after

Necropsy Findings

3 of the 5 patients who died within 5 days of the operation came to necropsy In 1 the fossa was empty, and in 2 there were small fragments of pituitary tissue In 1 patient who died two weeks after the operation a very thin subcapsular rim of apparently viable cells, deep to much necrotic tissue, was seen The full effects of irradiation would not be apparent at this time In 1 patient who died twelve weeks after the operation very small islands of apparently viable cells were found within a nodule of fibrous tissue

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DISCUSSION

Our main purpose was to find a method by which the pituitary gland can be destroyed completely in all (or nearly all) cases Evidence of complete destruction depends in the last resort on careful examination of the pituitary fossa post mortem This evidence is hard to obtain, because most of these patients subsequently die at home Endocrine tests provide partial information only We are supplementing those which we have already used with other methods, including estimations of œstrogens in the urine

It may be that an optimal therapeutic effect can be obtained by partial destruction of the pituitary gland and that elaborate measures to destroy it completely are unnecessary This will not be decided until large parallel series of cases are available for comparison The proportion of patients in our series who show objective evidence of remission after operation is higher than that in previously published series This may indicate that the degree of destruction of the pituitary gland influences the result, and that the method which we are using is more effective than either surgery or irradiation alone The remissions have been striking, and the patients have seemed to improve in every way

The observation that those with blood-borne metastases respond to operation, whereas those with local disease alone do not, may be significant It is dangerous to draw conclusions from such small numbers, particularly since it is never possible to exclude for certain the presence of distant metastases Nevertheless, if we take the figures at their face value, the probability of such a difference being due to chance is 1 285*

Another difference which we have observed may be relevant Those with blood-borne metastases have depressed thyroid function preoperatively, whereas those with local disease alone have normal function [10]

SUMMARY

A method is described for attempting to destroy the pituitary gland completely by surgical hypophysectomy followed by intrasellar irradiation with yttrium-90 oxide in wax

Of 25 patients with advanced mammary carcinoma so treated 20 survived operation and 16 were greatly improved

We wish to thank Dr W T E McCaughey, of the department of pathology in Queen's University, for the necropsy findings, Dr A R Thompson, of the isotope division, Atomic Energy Research Establishment, for his great help and cooperation in preparing the yttrium wax mixture, Prof G M Bull for the use of counting apparatus, house-surgeons and nurses, particularly Sister F M Donaldson, for their help, Miss L Irwin for radiographs, Mr H. O Nevin and his staff for technical assistance, and the Northern Ireland Hospitals Authority and the Royal Victoria Hospital management committee for financial help

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* If the incidences of remission in the 2 groups (0/3 and 16/17) are compared, exact P (single tail)=0·0035

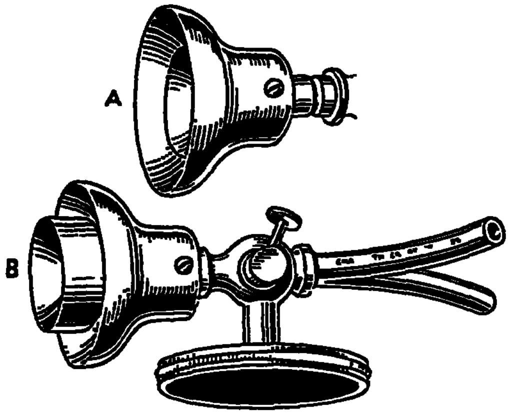
10 Edelstyn G A, Lyons, A R, Welbourn R. B *Lancet*, 1958 (in the press)

New Inventions

AN IMPROVED STETHOSCOPE

The great variety in design of stethoscopes on the market indicates a remarkable diversity of opinion on their relative merits Research on the efficiency of the simple acoustic stethoscope has been backward and the application of the scanty information available has been slow

Rappaport and Sprague [1] have pointed out that the volume of air in the system should be kept to a minimum The tubing should be as short as is practicable, and the optimum bore is $^1/_8$ in It follows that the chestpiece should be shallow, though not so shallow that it is blocked by the bulging of flesh into the bell The superiority of the bell for the low frequencies and the diaphragm for the high (by filtering out the low frequencies) has led to the general adoption of a stethoscope incorporating both chestpieces The principle that the larger the chestpiece the greater the volume of sound picked up by the stethoscope has been applied to the diaphragm chestpiece, which usually measures $1^1/_2$ in in diameter, but not to the bell, which tends to remain small The relative low sensitivity of the small bell has led to the wider use of the large diaphragm chestpiece, particularly when fitted with a thin diaphragm (or no diaphragm) allowing more of the low frequencies to pass, the advantage of a thick diaphragm to suppress the low frequencies, for concentration on the high, is then lost It would be logical to increase the diameter of the bell up to that of the diaphragm chestpiece, but there is then difficulty is making good contact on thin bony chests and localising murmurs in children Two sizes of bell may be carried but the changeover is inconvenient and the loose chestpiece is liable to be lost.



This difficulty can be overcome if the outer rim of a large bell can be made to slide up, leaving a smaller inner bell to make contact with the skin This was devised by Mr A M Stewart, and a prototype incorporating all these principles was made in the workshops of St George's Hospital It is now manufactured by Messrs Chas F Thackray (Park-street, Leeds, 1, and 38, Welbeck-street, London, W 1) The upper illustration (A) shows the outer rim pushed forward to its limit of movement to provide a large bell, and in the lower diagram (B) it has been pushed back to bring the small inner bell into use A simple friction device is incorporated in the outer bell to prevent accidental movement backward and forward The bore throughout the system, including the head frame, has been kept to $^1/_8$ in., and the lower end of the head frame has been angled forwards to make it more convenient to use short lengths of rubber tubing (e.g, 10 in.)

St. George's Hospital, London, S.W 1 — Aubrey Leatham
M.B Cantab, F.R.C.P

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Reviews of Books

Microtechniques of Clinical Chemistry for the Routine Laboratory

SAMUEL NATELSON, SC M , PH D , chairman, department of biochemistry, Rockford Memorial Hospital, Rockford, Ill Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 484 82*s* 6*d*

MOST of the routine methods of clinical chemistry are microtechniques in that 0 1–2 0 ml of blood is required for the estimation of a compound which may be present in a concentration ranging from only 1 mg or so to a few hundred mg per 100 ml The refinements which enable several analyses to be performed on the small amount of blood readily obtainable from an infant's heel extend the subject into the realm of ultramicroanalysis, and indeed this book evolved from a pamphlet with that title

Dr Natelson first describes the principles of ultramicrochemistry and the practical details of micromanipulation and accurate measurement of very small volumes, adding an account of their precision and accuracy He gives useful descriptions of microbalances (many of which, however, are models obtainable only in the United States) and of a wide variety of procedures, mostly, but not all, modifications of existing techniques of clinical analysis Special notes after each description draw attention to particular points and difficulties, and a list of the reagents required and a remarkably complete set of references are added

The methods described are good and are clearly based on wide experience, they include relatively recent clinical applications, such as the spectrophotometric determination of barbiturates and of vitamin A before and after ultraviolet oxidation It may surprise some to find the Folin-Wu method as well as that of Nelson and Somogyi for the estimation of glucose In the first method, the effect of time on the intensity of colour is too great for satisfactory spectrophotometry It is surprising too that fat is estimated on dried fæces and that no indication is given of the importance of determining the total daily output of fat in the stools

Though some of the methods are not customarily used in this country (e g , the glycerophosphate substrate method for phosphatase), the book gives guidance which every chemical pathologist and clinical chemist needs from time to time—namely, advice about the ways in which standard methods are cut down in scale and the difficulties that may arise We hope enthusiasm for ultramicrotechniques will not prompt a return to the analysis of capillary blood samples, not all of which are free from hæmolysis and contamination by tissue fluid, but provided this drawback is not forgotten the book has much to commend it to every department of clinical chemistry

Non-venereal Syphilis

ELLIS HERNDON HUDSON, M D , F A C P , emeritus professor and director of health, Ohio University, Athens, Ohio London E & S Livingstone 1958 Pp 204 30*s*

THIS book was written in the hope that it would interest readers ranging from specialists in syphilis to lay health workers and sociologists To achieve his object Professor Hudson has been forced to adopt the style of a popular digest, but this should discourage no-one, not even the expert venereologist He is predominantly concerned with his experiences of bejel, a non-venereal syphilis endemic in some areas of Iraq In addition, he puts forward much evidence in support of the view that venereal syphilis, bejel, yaws, pinta, and endemic syphilis are different clinical entities all of which are caused by the same organism, *Treponema pallidum* For this group of diseases he uses the term "treponematosis" and shows how climatic and sociological factors are largely responsible for the clinical manifestations of the disease The full description of bejel and its relationship to *franji* (the local Iraqi name for venereally acquired syphilis) contains 78 excellent and informative photographs of various lesions of bejel The serology and microscopic and experimental pathology of the disease are dealt with briefly and the book ends with the treatment used in the pre-antibiotic era

This readable and thought-provoking monograph should be studied by all who are interested in treponemal diseases

Biochemical Contributions to Endocrinology

Experiments in Hormonal Research SIR CHARLES DODDS, M D , F R C P , F R S Stanford, California Stanford University Press London Oxford University Press 1957 Pp 76 18*s*

THESE five lectures given by Sir Charles Dodds at Stanford University, California, in 1956 describe work which he and his colleagues of the Courtauld Institute have initiated or been connected with during the past thirty years or so The account of the discovery of stilbœstrol cannot fail to be exciting, and it makes the rest of the book seem a little pedestrian The book suffers from the fact that it had to be divided into five lectures of set length, and one rather disconcerting result is that the chapter entitled Agricultural Applications of Synthetic Œstrogens contains a detailed account of the discovery of the adrenal cortical hormones This section seems in error at one point when it states that Swingle and Pfiffner prepared their classical adrenal extract in Great Britain Other topics discussed are the polynitrophenols and their effects on oxidation, and the possible action of posterior pituitary hormones on gastric secretion A final chapter describes the discovery of aldosterone

The many admirers of Sir Charles' work will be glad to have this compact synopsis

Annual Review of Microbiology

Vol XI Editors C E CLIFTON, S RAFFEL, and R Y STANIER Palo Alto, California Annual Reviews 1957 Pp 536 $7 50

THE number of review articles continues to increase at a nearly logarithmic rate, and more and more research-workers derive great benefit from writing reviews of their current subject of investigation The reading public for reviews, however, may shrink gradually unless the editors are strict in their choice of subject The eleventh volume of the microbiology review has been well chosen and will appeal to a great many readers It ranges widely from colicins and virus diseases of animals and plants through various aspects of bacterial metabolism to bacterial and protozoal genetics and homograft reactions

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Instrument Encyclopedia (London Herbert Publishing Co 1958 Pp 292 63*s*)—In consultation with Mr A Linford, Mr E W Battey, editor of *Instrument Review*, has compiled a concise means of reference to the materials used and produced in the instrument and allied industries There is a glossary of definitions and terms in common use in instrument technology, an alphabetical list of manufacturers, a geographical list of overseas agents, and a buyers' guide This guide is classified according to branch of technology, thus, the section entitled "Laboratory—medical—research" contains an alphabetical list of instruments (from absorptiometers to zoology laboratory apparatus), each entry giving the names of manufacturers supplying it The book ends with an alphabetical list of trade names, giving the supplier of each item The medical interest of the book is limited but it may be of use in laboratories to whose who wish to know the supplier of an instrument they need

Modern Treatment Year Book (London Baillière, Tindall, & Cox 1958 Pp 307 27*s* 6*d*)—Sir Cecil Wakeley has assembled 31 articles, designed for the family doctor, on current practice in common conditions in all branches of medicine Notes on basic science and diagnosis are included in appropriate places The teaching is practical and sometimes iconoclastic, thus, Mr W P Greening says "There is only one clinical finding in breast cancer the presence of a lump in or near the breast," and Mr Philip Reading "The only instance where ear drops had any striking effect is recounted by the Ghost in *Hamlet*"

THE LANCET
LONDON 1 MARCH 1958

Bed Rest, Thrombosis, and Embolism

The various methods of treating established post-operative venous thrombosis[1] are in a sense all confessions of failure—evidence "that we have sadly missed the boat in our prophylactic treatment".[2] The pathological basis of the prophylactic regime was investigated by Gibbs.[3] He carefully dissected the veins at necropsy on 253 hospital patients, whose period of confinement to bed before death was accurately known. This study confirmed the high prevalence of clinically unsuspected leg-vein thrombosis[1 4-7]—and postmortem phlebograms partly explained its frequency.

With advancing years the intramuscular veins of the calf, especially those of the bulky and powerful soleus, increase in diameter, number, and tortuosity. Essential for efficient drainage when the muscle is at work, this venous network is functionally redundant at rest. Its emptying depends on muscle contraction, and at rest, since its delicate walls are ill suited to withstand rising pressure, it gradually fills and becomes distended with blood. Pooling is further encouraged by local currents set up by abrupt changes in diameter, and by the anatomical pattern of the vessels. Unlike the intramuscular veins of the gastrocnemius (which drain directly into the posterior tibial and peroneal trunks) the soleus veins form a series of vascular arcades. When the leg is horizontal and the muscle is relaxed, gravity promotes back-flow and stagnation in these inverted arches.

A similarly favourable site for pooling is the confluence of several large veins near the upper end of the thigh. During muscular activity these streams, all travelling at different speeds, mingle and pass rapidly into the common femoral and external iliac vein. At rest, however, the flow slackens, surrounding muscles weigh heavily on the main channel, and tiny whirls are stirred up by the valve cusps guarding the venous ostia. Possibly in certain body positions the inguinal ligament—like the adductor opening lower in the thigh—adds a compressing force.

Gibbs challenges the widely held view that thigh-vein thrombosis arises as a direct extension from the leg.[8-10] It is true, he says, that thrombosis is usually found affecting both sites (more commonly the legs), but partial or complete obliteration of the femoral vein would in itself cause stagnation and lead to clotting in the peripheral column of blood. The more frequent distal localisation of the symptoms and signs certainly does not preclude this possibility: "the presence of extensive thrombosis with resultant stasis of the venous return will result in a gradient of relative anoxia throughout the limb, which will be most severe in the periphery".[3] In all cases where Gibbs found direct continuity between the femoral-vein and leg-vein thrombus, the clot extended along the whole length of the thigh, none was discovered "in the act of propagation". (This mode of spread has been observed on phlebograms[9]; Gibbs's findings merely suggest that it may be rare.)

To elucidate the natural history of thromboembolism, it is still necessary to rely on postmortem appearances, and, though this has been a battlefield of the best minds in pathology since Virchow,[11-14] their interpretation remains as controversial as ever. Gibbs paid especial attention to the time-relationship of the intermediate stages, and he found the naked-eye picture a wholly unreliable guide. Microscopically the thrombus begins to undergo degenerative changes almost as soon as it is formed, and within twenty-four hours dead and dying white blood-cells impart to it a characteristic appearance. A foreign-body reaction is provoked in the adjacent vein wall, and signs of organisation can be detected as early as the fourth day. Hæmosiderin particles from disintegrating red blood-cells can be spotted before the end of the first fortnight; and, though organisation may take years to become complete, it is well advanced after a few months. Examination of a large number of thrombosed veins showed, moreover, that organisation starts earliest around the valve cusps, where the thrombi are composed predominantly of white blood-cells, platelets, and fibrin, and that commonly it is delayed in the nearby red thrombi. Since the selective deposition of the formed elements of the blood-stream depends mainly on the speed of flow, the usual explanation—that white thrombi represent earlier deposits—is not entirely satisfactory. Gibbs believes that the local currents and eddies around the vein junctions favour the formation of a white thrombus, while the slowly moving main stream tends to deposit red thrombi. Their different cellular composition determines their capacity for retraction. The unretracted or only partly retracted white thrombus exercises a powerful pull on the vein wall and may lead to its ultimate collapse during organisation. The re-formed vessel will then be represented by a thin fibrous cord, pierced by minute secondary channels, and, since the segment around the valve cusps is the part most commonly involved, this vessel is likely to prove an inadequate and incompetent substitute for the old one.

The cases investigated by Gibbs were both medical and surgical. Charted against the duration of bed rest, a curve representing the incidence of lower-limb thrombosis begins its steep ascent within the first three days, it reaches its high point at two to three weeks, and it maintains a steady high level after that. The incidence of thigh-vein thrombosis can be traced along an approximately parallel curve, except for a spike at four to five weeks' bed rest. Pulmonary embolism was most commonly found in patients who died after two to three weeks in bed. From a detailed analysis Gibbs concludes that continuing bed rest is the only ætiological factor which can account for such patterns, and he implies that

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1. *Lancet*, 1957, ii, 1101.
2. Rivlin, S. *ibid*, p. 1290.
3. Gibbs, N. M. *Brit. J. Surg.* 1957, 45, 209.
4. Rössle, R. *Virchows Arch.* 1937, 300, 108.
5. Belt, T. H. *Amer. J. Path.* 1934, 10, 129.
6. Frykholm, R. *Surg. Gynec. Obstet.* 1940, 71, 307.
7. Neumann, R. *Virchows Arch.* 1938, 301, 708.
8. Hunter, W. C., Krygier, J. J., Kennedy, J. C., Sneeden, V. D. *Surgery*, 1945, 17, 178.
9. Bauer, G. *Acta chir. scand.* 1941, suppl. 74.
10. Martin, P., Lynn, R. B., Dible, J. H., Aird, I. Peripheral Vascular Diseases. Edinburgh, 1956.
11. Virchow, R. Cellular Pathology. London, 1860.
12. Zahn, F. W. *Virchows Arch.* 1875, 62, 81.
13. Samuels, P. B., Webster, D. R. *Ann. Surg.* 1952, 136, 422.
14. Hadfield, G. *Ann. R. Coll. Surg. Engl.* 1950, 6, 219.

other ætiological agents are of doubtful importance Yet many features of thromboembolism suggest an imbalance between thrombogenic and antithrombogenic influences in the blood itself[1 15-17], and opinions about the importance of primary endothelial damage are still fluctuating On the one hand the dual concept of phlebothrombosis and thrombophlebitis (enthusiastically hailed a few years ago) has failed to stand up to the test of the antibiotic era, and confirmation of Virchow's view that endothelial abnormalities are rarely demonstrable in fresh thrombi has come from many sources There is, on the other hand, growing evidence that indirect injury—such as inadequate blood-flow in the vasa vasorum or denervation—can cause changes in the vessel wall which lead to the deposition of minute platelet thrombi along its intercellular cement lines[18 19] Clinically the close relationship between gross trauma and thrombosis remains to be clarified[20]

Leg-vein thrombosis, unpleasant though its local after-effects can be, would hardly warrant so much argument were it not for its one formidable complication—pulmonary embolism It is now realised that some patients survive even massive embolism, while others are killed by relatively small emboli which spread locally, precipitate circulatory disturbances, or predispose to infection (A few patients succumb many years later to chronic cor pulmonale[5]) Gibbs contends that the majority of pulmonary emboli arise not from the calf veins but from primary thromboses in the femoral vein Arguments for this thesis are the frequent coexistence of femoral-vein thrombosis and pulmonary embolism, their suggestive time-relationship, and the strikingly close "femoral fit" of many pulmonary clots A more circumstantial piece of evidence is the notoriously high incidence of thromboembolism after pelvic operations Gibbs believes that hip flexion, which these operations frequently entail, distorts the femoral vein in the groin and promotes venous stasis and thrombosis The greatest weakness of all such theories (as Gibbs himself emphasises) is their foundation on postmortem studies Leg-vein thrombosis is not an agonal process, the postmortem picture gives little indication of the mode and time of detachment of an embolus, and even an unselected necropsy series represents a small, highly selected, and perhaps atypical, group of patients

We cannot, in fact, expect to define the mechanism of thromboembolism until we can study it in greater detail during life, and this we cannot do without greater accuracy in diagnosis Even the most watchful observer may either miss three out of four cases of thrombosis or (if he is thrombosis-minded) mistakenly diagnose three for every real one This clinical uncertainty underlies the need for regarding all bed patients as potential cases of thrombosis and for treating them all prophylactically. Every thoughtful surgeon will endorse Ritlan's warning[2] that prevention of venous stasis, which is at present our only effective therapeutic weapon, is not necessarily effected by early ambulation alone Confronted with the alarming complexity of human disease, the modern surgeon is as prone to fetishism as his cave-dwelling ancestor, and "getting the patient out of bed" is rapidly becoming one of his favourite totem-poles The analogy of joint movements springs to mind the old lady in the Colles plaster, ineffectually wiggling her swollen fingers, is as pathetic a sight as the old gentleman shuffling around his bed the day after his prostatectomy "Movement", like "ambulation", can mean anything, and it is often left to the patient to interpret them This is the more unfortunate since many advances in surgical and ancillary techniques carry the penalty of an increasing likelihood of postoperative complications, and particularly of leg-vein thrombosis Advanced years, a long time spent on the operating-table, artificial slowing of the circulation, and complete muscle relaxation are some of the thrombogenic influences which must be offset by attention to the prophylactic routine The apparatus suggested by Owen Williams[21] is a useful aid, but it is not intended to be the whole answer The ritual must begin the moment the patient is put to bed on admission (without his sheets tucked tightly under the mattress), it must follow him on his stretcher journey to the theatre, it must protect him as he floats limply between stretcher and the operating-table, it must inspire the hand which temporarily deprives him of his muscle-power, and it must guard over him as (hour after hour) he lies acrobatically suspended in poles, hooks, and slings Its arch-priest may not rest content until he has earned the accolade of fusspot

Auto-antibodies

It has long been believed that the individual organism does not form antibodies against its own antigens This ability to distinguish the native from the foreign has not been fully explained, but Burnet's[22] hypothesis of the self-marker helps to create a clearer mental picture. Burnet has suggested that in any individual the antigens carry a self-marker by which they are recognised and hence ignored by the antibody-forming cells Derangement of this mechanism could be expected to result in the production of auto-antibodies, and it is hard to understand the widespread reluctance to acknowledge that auto-antibodies may be formed and that they may have a pathogenic role

Recent work has considerably weakened the doubters' case Studies of the autohæmolytic anæmias[23] and of the anti-thyroid antibodies in Hashimoto's disease[24] have clearly shown not only that auto-antibodies develop in man but also that their presence can be associated with a disease-process involving the antigenic organ concerned Experimental support has not been lacking,

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15 Moolton, S E , Vroman, L , Vroman, G M S , Goodman B *Arch intern Med* 1949, 8, 667
16 Allen, E A , Barker, N W , Hines, E A , Peripheral Vascular Diseases Philadelphia, 1955
17 Proceedings of the 1st International Congress on Thrombosis and Embolism Basle, 1955
18 O Neill, J N *Ann Surg* 1947, 126, 270
19 Impallomeni, G , *in* Proceedings of the 1st International Congress on Thrombolism and Embolism, Basle, 1955
20 Hamilton, T R , Angevine, D N *Milit Surg* 1946, 99, 450
21 Owen Williams, G E *Lancet*, Jan 18, 1958, p 166
22 Burnet, F M , Fenner, F The Production of Antibodies Melbourne, 1949
23 Dacie J V The Hæmolytic Anæmias London, 1951
24 Riott, I M Doniach, D , Campbell, P N , Hudson R V *Lancet*, 1956, ii, 820 See also ibid. 1957, i, 1075

and such conditions as allergic encephalomyelitis[25] or thyroiditis[26] produced by injecting an emulsion of the appropriate organ with adjuvants are almost certainly the result of an auto-immunological reaction The link between auto-antibodies and disease is most clearly evident in the "collagen" diseases Thus both the Rose-Waaler factor, which is responsible for positivity in the sheep-cell agglutination test for rheumatoid arthritis,[27] and the serum factor in disseminated lupus erythematosus, which is responsible for the L E cell phenomenon,[28] have many of the characters of auto-antibodies Moreover, it is in this group of diseases that Gajdusek[29] found the highest incidence of a serum factor capable of fixing complement in the presence of extracts of various organs, notably the liver and kidney

In a series of 496 patients whose sera were studied for the presence of auto-immune complement-fixing (A I C F) antibodies, Gajdusek found a significant number of positive sera in four groups—namely, those with liver disease, "collagen" disease, paraproteinæmias, and miscellaneous unrelated diseases High titres (exceeding 1 in 1000) were found only in infective hepatitis, primary biliary cirrhosis, disseminated lupus, and macroglobulinæmia A remarkable feature of this A I C F antibody reaction is its lack of either organ or species specificity Thus, though there was some variation in the titre of any one serum with the various organ extracts used, this was relatively slight, and the titres with rat-organ extracts did not fall significantly below those with the corresponding human organs A similar lack of species specificity is shown by the serological factors underlying the L E-cell test of disseminated lupus[7] and the sheep-cell agglutination test of rheumatoid arthritis[6] Apparently in each of these three examples the antigenic structure against which the serological factor is directed is common to a wide range of animal tissues and species

Little, if anything, is known of the way in which such antigens excite an auto-antibody response, or, alternatively, why such a response is not universal Three hypotheses seem worth considering firstly, that in normal animals the antigen has not access to the cells that form antibody, secondly, that in the native state antigenicity is lacking, antigenicity requiring some alteration brought about by toxic or enzymatic action, and thirdly, that the reacting agents (in Gajdusek's tissue extracts, for example) are not complete antigens but only haptens, capable of reacting with antibody but unable to stimulate its production until linked to an exogenous protein to which they impart their own immunological specificity[30]

The frequency with which Gajdusek found positive reactions in patients with hepatitis is of the greatest interest The extreme unpredictability of the course of this disease is well known Can it be that auto-immune reactions play a role in the development of chronicity? The very high proportion of positive reactors in the group with chronic active hepatitis suggests that this may be so But the alternative question must not be overlooked—namely, is the damaged liver with its mass of Kupffer cells especially sensitive to auto-antigenic stimulation? An attempt to correlate the clinical status of the patient with the A I C F antibody titre failed to establish anything significant For example, a patient with disseminated lupus may have a high A I C F antibody titre with kidney antigen in the complete absence of renal involvement, or a low titre with renal involvement This is by no means surprising With the possible exception of auto-hæmolytic anæmia, none of the natural or experimental diseases attributable to auto-immune reactions show any correlation between the amount of circulating antibody and the severity of the disease Possibly the circulating antibody is to be regarded as an epiphenomenon, the lesions themselves resulting from cell-fixed antibody such as is responsible for tuberculin sensitivity or homograft immunity

Annotations

AN UNIDENTIFIED ILLNESS

Towards the end of January there was a brisk increase in the demand for children's beds in London hospitals an outbreak of an acute and often alarming respiratory illness in young children was responsible A similar wave appeared about the same time in Birmingham No connection has been established between this disease and any type of influenza virus and the cause has not yet been identified Laboratory investigations are proceeding It seems likely that the infection (if such it is) is the same as that which appeared in London, Liverpool, Manchester, and elsewhere in 1953 and which defeated efforts to identify it[1 2]

On p 482 we give details of experiences in the past few weeks at the Princess Louise Kensington Hospital for Children where 104 children were admitted with this "acute respiratory disease" between Jan 20 and Feb 19 In a typical case, after a few days with a "cold," the child began to have difficulty in breathing, he might be pale, shocked, and cyanosed, and a white frothy secretion in the mouth and pharynx needed frequent aspiration From this seemingly grave state he could usually be rescued by oxygen and careful nursing, and the number of deaths has been small Chest radiographs taken after the acute phase had passed showed collapse or consolidation in upper and lower zones, but these lesions seem to be shortlived The severity of the illness justified the giving of antibiotics to all the children admitted to the Princess Louise, but it seems doubtful whether they hastened recovery from the primary illness

In its mild forms this condition is unlikely to attract much attention, and in the absence of unusual respiratory distress they may not be regarded as anything out of the ordinary The disease may be widespread and unrecog-

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[25] Kabat E A Wolf, A Bezer A E *J exp Med* 1949, 89, 395
[26] Witebsky E, Rose N R *J Immunol* 1956 76, 408
[27] Glynn L E, Holborow, E J, Johnson G D *Proc R Soc Med* 1957, 50 469
[28] Franklin E C Holman, H R, Muller Eberhard H J *J exp Med* 1957 105 425
[29] Gajdusek D C *Arch intern Med* 1958 101 9
[30] Liu C T McCrory, W W Fluck, J A *Proc Soc exp Biol*, N Y 1957, 95, 331

[1] Ministry of Health Annual Report of the Chief Medical Officer, 1953, p 45
[2] Heycock, J B, Noble, T C *Brit med J* 1956, i, 438

-nised in this country at present and it may have been so for some time past. The investigation of an illness so hard to label is particularly arduous during a winter when the respiratory complications of influenza (described this week in an article by Dr. Grant and his colleagues on p. 449) are much in evidence.

PERINATAL MORTALITY

EVERY year in England, Scotland, and Wales about 18,300 babies are stillborn and a further 11,500 die in the first week of life. This figure of 30,000 perinatal deaths does not improve much, and three years ago the National Birthday Trust Fund set up a committee to investigate. Valuable information could, their committee thought, be obtained from a nation-wide survey in which, over a certain period, every mother, midwife, and doctor concerned with a live birth or a perinatal death would take part. A questionary was accordingly prepared (with due regard to the fact that it will yield more accurate information on social and administrative features than on clinical ones), and this was pruned, improved, and then tested in two pilot surveys—in Nottingham and in parts of south-west England. The final version, as approved by the committee—which represents obstetricians, pædiatricians, practitioners, statisticians, pathologists, public-health officers, Ministry representatives, midwives, and nurses—has been kept as short and simple as possible, but inevitably it will mean extra work. This will fall especially on the midwives, who are asked to fill in the first part by "interviewing" the mother, usually on the day of the birth, and will fill in other details during the puerperium, with the help of doctors when necessary. Only by including social conditions, past obstetric history, booking arrangements, antenatal care, methods of delivery, and the circumstances and pathology of the perinatal deaths can a full picture be provided.

A questionary will, it is hoped, be filled up for every birth in England, Scotland, and Wales between March 3 and March 9. During this period there are likely to be about 13,500 live births and 500 perinatal deaths—the latter being defined, for present purposes, as stillbirths and deaths in the twenty-eight days following delivery. But to ascertain satisfactorily the features associated with perinatal death and to compare these features with those found in 13,500 survivors, 6000 cases are required. Accordingly, all perinatal deaths in March, April, and May will be followed up by the questionary. Furthermore, it has been decided that for special histological and virus studies 2000 postmortem examinations in cases of perinatal death during March shall be conducted in regional centres. The committee is grateful both to those pathologists who have agreed to do this extra work and also to those others who are handing on material that might have been interesting to themselves.

It says much for the organisation, and for the spirit of cooperation in this matter, that nearly all authorities contacted—local health authorities, regional boards, teaching hospitals, pathologists, and coroners—have agreed to join in the task. The fact that the inquiry is on a national scale does not mean that it takes the place of the valuable local researches already in progress. But the addition of fresh data from large numbers of people may make it possible to see more clearly the directions most likely to lead to a reduction of perinatal mortality—a reduction comparable, we may hope, to what has already been achieved in maternal mortality.

RESCUE FROM THE AIR

FEW of us bother to raise our eyes towards a passing plane, but the helicopter is still an attractive curiosity. Its unrealistic appearance, a clownlike element, a hint of flying saucers, may partly explain why we do not take helicopters as seriously as we should. Outside the genius of our aircraft industry and the Services, as an island race we seem quaintly slow to become airminded.

On another page of this issue Flight-Lieutenant Edwards describes some of the rescue techniques used with the Bristol Sycamore helicopter. This aircraft offers much better opportunities for medical transport than the earlier types, where it was not always possible to stow the whole of the patient inside the cabin. (It is not given to many of us to retain much peace of mind while slung in the slipstream.) Both the Royal Air Force and the Royal Navy have built up a fine standard of efficiency with their helicopters. Each year adds to their roll of achievement in lifesaving and the relief of suffering for Servicemen and civilians alike. This valuable service has been developed in some areas to be an integral part of the local distress plan. For example, a North Wales newspaper published an advertisement[1] inviting the general public to telephone R.A.F. Station Valley, Anglesey, for helicopter help in searching for lost children, evacuating ill people from difficult places, rescuing climbers, swimmers, and shipwrecked sailors, and saving those cut off by the rising tide. Ten minutes' readiness, $1^1/_2$-miles-per-minute flight to any scene within 35 miles' radius, cheerful acceptance of false alarms if the mistake is genuine—that is Service indeed. No doubt similar offers are made from R.N., R.A.F., and U.S.A.F. stations elsewhere.

Westland Dragonflies, Whirlwinds, and Widgeons and Bristol Sycamores have pioneered aerial rescue work around our British coasts. The American Forces have also helped with their Service helicopters in various emergencies—notably the wreck of the Goodwins lightship. For high-altitude work in the Alps special patterns have been evolved, such as the Sikorsky models and the French turbo Alouette, and the use of both was illustrated dramatically in the Mont Blanc tragedy a year ago.[2]

It would be unwise to be too starry-eyed about helicopters. They have their limitations. Night flying can be tricky if not actually dangerous. The helicopter can hedge-hop below the cloud base where conventional aircraft would be useless, and in sea rescues the SARAH radio homing device on dinghies or Mae Wests helps to pinpoint the casualty. But flying in winds over 45 knots is difficult, and work in the mountains, apart from problems arising from altitude rarification, introduces the hazards of vertical air currents and eddies. A lot depends on good ground-to-air communication. Helicopters fitted with V.H.F. radio cannot talk direct to most ships. Some of the Royal National Lifeboat Institution craft have been fitted with V.H.F. sets, but otherwise messages may have to pass along a chain of G.P.O. coast radio stations, coastguards, landlines, and flying-control stations with chances of delay and distortion. Direct visual communication with Aldis lamps and the like is often not possible in civilian accidents. Some of the most vital messages may be the minute-by-minute orders on the spot. We seem to have a lot to learn.

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[1] *Caernarvon and Denbigh Herald and North Wales Observer*, Aug. 31, 1956.
[2] *Paris Match*, Jan. 12, 1957.

We still tend to think of the helicopter finishing its job when the patient has been delivered to the waiting ambulance on the shore or at the airfield Surely we should think much faster, and see that a helicopter landing-site is arranged alongside every major hospital Various Cornish hospitals were reported to be doing this,[3] and no doubt there are others in the country besides those mentioned by Dr Edwards The time cannot be far off for a landing-ground to be a " must " for the self-respect of every management committee

Rescue by helicopter calls for knowledgeable cooperation by the rescued, people need to know something about the drill if they are to be prevented from chopping their heads off on tail rotors, falling out of strops, burning themselves on exhausts, capsizing their sailing-boat under the down-draught, and entangling the rescue cable in their backstays Such avoidable misadventures not only add to the difficulties of rescue but further imperil the lives of the aircrew There are notes for sailors[4] in areas where helicopters operate, but it seems that more widespread guidance might help Recent television programmes have included helicopter mock rescues as an entertainment feature, and there may be scope in this medium for a more educational approach We never know when we may be thankful for help from the skies

The Armed Services are the main source of helicopter help in Britain, but many other countries have developed aerial aid by civilian enterprise La Garde Aerienne Suisse de Sauvetage (G.A S S), set up in Zurich in 1952, is supported by voluntary effort[5] G A S S offers to help in air accidents, avalanches, landslides, and floods, as well as sailing and road accidents It is essentially an auxiliary service to be called out by the normal rescue authorities It can provide planes, helicopters, and parachute teams who are all trained volunteers Blood-transfusion can be brought direct to the patient, and even search dogs can be flown in G A.S S already has a fine record of achievement, ranging from the simple airlift of a seriously injured woodcutter between a remote hillside and hospital, within six minutes, to the evacuation of the victims from the tragic avalanches at Vorarlberg in Austria The United States called on help from G.A S S when two airliners collided in 1956 over the Grand Canyon, falling in a most inaccessible place Aerial rescue is assuming an increasingly important role in many other countries Soon it will be almost world-wide

CLINICAL GERIATRICS

THERE are probably no diseases peculiar to old age, but the care of elderly people is associated with special problems, some of which have been reviewed by Anderson[6] For instance, in the aged, history-taking is liable to be more difficult, and symptoms and signs less obvious, than in younger patients A fractured femur may cause only slight weakness in the affected limb after a fall, cardiac infarction may result in only a little breathlessness or faintness, and acute appendicitis may lurk behind mild abdominal pain

Mental confusion is an alarming symptom which usually precipitates a domestic crisis Where the onset is sudden it is often symptomatic of some acute physical disturbance such as pneumonia, urinary infection, cardiac infarction, a cerebrovascular accident, or dehydration Sometimes it is due to a change of environment, and occasionally to drugs—especially bromides, hyoscine, and barbiturates Nocturnal restlessness and wandering are commonly due to reversal of sleep rhythm, and the more active an old person can be kept in the day time the better is his chance of a quiet night.

Urinary and fæcal incontinence is a distressing problem in the home and a common cause of admission to hospital Incontinence of urine is sometimes due to a remediable local cause such as cystitis, prolapse, or prostatism, and sometimes to a central cause such as cerebral thrombosis or an emotional upset The polyuria of diabetes and chronic nephritis may also cause incontinence The trouble is always worse in patients confined to bed, and is sometimes cured by getting the patient up Fæcal incontinence is less common and more distressing, but fortunately more remediable It is often due to fæcal impaction, aggravated by apathy and bedfastness Impaction of fæces in the rectum is potentially fatal, and it is often unrecognised It may present as rectal discomfort, as abdominal pain with vomiting, as fæcal incontinence, or as diarrhœa constipation is seldom absolute. The diagnosis is readily made by rectal examination, and repeated enemas, sometimes after initial manual removal, relieve the condition

Hemiplegia due to cerebral thrombosis is one of the commonest geriatric problems, but the extent to which most hemiplegics can be reabled needs to be more widely known Early passive movement followed by bed-end exercises and walking between parallel bars or with a walking machine are the foundation of treatment A toe-spring or calliper with a heel-stop is a useful aid to prevent foot-drop All this contributes to the maintenance of activity, which is a fundamental principle of geriatric care " The successful doctor and nurse of the elderly are those who help their patients to die with their boots on "[7]

DIAGNOSIS OF BRONCHIECTASIS

THE anatomical extent of bronchiectasis can be accurately assessed in life only by bronchography, and the usefulness of this investigation has increased with the introduction in the past few years of new contrast media that are rapidly cleared from the lungs Opinion is less unanimous about the diagnostic value of a plain chest film In 112 patients in whom the diagnosis was established bronchographically Gudbjerg[8] found that only 7% had completely normal plain films 31% showed lobar collapse, unquestionably the most suggestive sign, 43% showed honeycombing, and no less than 85% showed increased lung markings This last figure must be treated with reserve because in the assessment of increased lung markings the subjective factor is immensely strong, particularly when the observer knows beforehand that the patient has proven bronchiectasis, but few will dispute Gudbjerg's conclusion that a normal plain film is on occasion compatible with severe bronchiectasis

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[3] Times Aug 25 1956

[4] Notes for Yachtsmen Sea Rescues by Helicopter Ministry of Transport and Civil Aviation February 1957

[5] Rev int Croix Rouge 1957 10, 593

[6] The Care of the Elderly Sick in General Practice By W F ANDERSON Publication no 9 of the Royal College of Physicians, 9 Queen Street Edinburgh 2. 1957

[7] Rudd, T N The Nursing of the Elderly Sick, p 15 London, 1953

[8] Gudbjerg, C. E. *Acta radiol*, *Stockh* 1957 suppl. 143

THE INDEX and title-page to Vol II, 1957, which was completed with THE LANCET of Dec. 28, is published with our present issue A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of THE LANCET, 7, Adam Street, Adelphi, W C.2 Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now

Special Articles

HELICOPTER RESCUE SERVICE

A G Edwards
M B Lpool
FLIGHT-LIEUTENANT, R A F

Since rescue and transport of patients by helicopter has come to the fore in recent years, an account on the rescue service from the medical viewpoint may be interesting and of instructional value

Helicopters were of much value in the removal of casualties from the jungle during the Malayan and Korean campaigns and from behind the lines where airfields were impracticable, and we are constantly reading in the daily press of their application in one form or another

There are several types of helicopter design, but basically all helicopters consist of a cabin with a large horizontal rotor above and a small vertical tail rotor at the rear Briefly, the horizontal rotor of variable pitch gives the lift to the aircraft in proportion to the amount of air passing through its disc The plane of the disc can be altered to permit forward, backward, and sideways motion The tail rotor, also of variable pitch and operated by foot pedals, is used as a rudder (if the natural effect of the torque is allowed to take place, this enables a turn to the left to be made, whereas overcorrection enables a turn to the right to be made) This account applies particularly to the Bristol Sycamore Mk XIV

The Bristol Sycamore (fig 1) can carry five persons—pilot, navigator, and either three passengers or one stretcher patient The cubic capacity of the space available for a stretcher and attendant is no more than about 65 cubic feet It was decided that, on all occasions where rescue of aircrew from the sea is concerned, the medical officer will not go with the helicopter, because this reduces performance with increase of weight (Therefore all aircrew were instructed in first-aid and later passed the examination for the St John Ambulance Association adult certificate) The patient will then be flown to the nearest hospital landing-field, of which several are in preparation (see below)

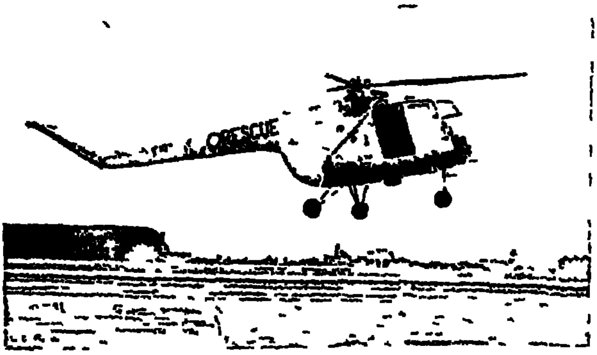

Fig 1—Bristol Sycamore

Equipment

The equipment carried by the helicopter is as follows

(1) *One Neil Robertson stretcher* (fig 2) —The main advantage of this stretcher is that it is light and provides excellent splintage for legs (below thigh) and chest The disadvantages are (*a*) slight spinal flexion when being carried by the stretcher bearers (there is slight extension on winching), (*b*) difficulty in including injured arms within their retaining strap, (*c*) pressure on the arms by lifting-cables, and (*d*) the stretcher and patient are not buoyant and if the cable parted when the stretcher was being lifted—e g , off a lifeboat at sea—the patient would be lost Also the patient must of necessity feel extremely anxious about the whole precedure because his arms are bound by the retaining strap For these reasons two modifications are being prepared for trial (*a*) the arrangement of a quick-release system for the arm-strap, which can be operated by the conscious patient and is based on the rip-cord principle, (*b*) buoyancy chambers surrounding the stretcher and operated by a static line from the lifeboat to two carbon dioxide cylinders The static line is to be 100 ft long and could be used for towing the patient back to the boat Although this form of rescue is purely lifesaving, the ideal is constantly borne in mind

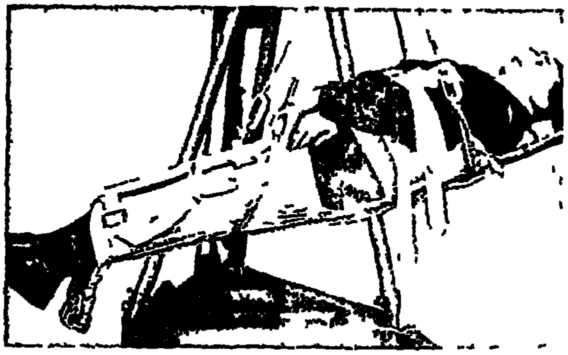

Fig 2—Neil Robertson stretcher

(2) *One Bristol stretcher* —This is a light collapsible stretcher of tubular 'Duralumin' It is used instead of the Neil Robertson stretcher where a patient is loaded into the aircraft while on the ground This lessens any discomfort to the patient Where there is no need for a medical attendant, a second stretcher can be stacked above the first, both stretchers being held in position by retaining bolts

(3) *One electric blanket* —This is quilted and insulated so that a person in wet clothing can be completely covered without risk of electrocution To reduce the risk of electrocution still further, the blanket is switched on during the time it takes for the aircraft to reach its destination, and switched off before the rescued person is put into it This also obviates the risk of overheating a shocked patient, and this point has been emphasised to the aircrew with whom I have had contact, so that they might attend the patient with this point in mind

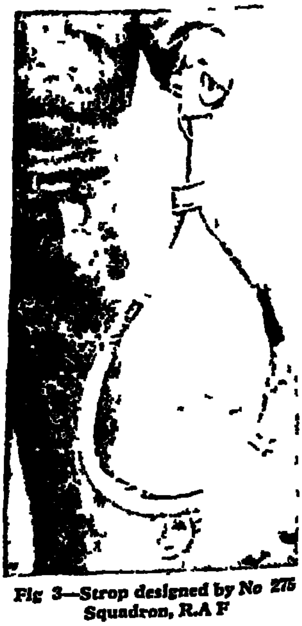

Fig 3—Strop designed by No 275 Squadron, R A F

(4) *A single strop* designed by No 275 Squadron (fig 3)

(5) *A single strop* designed by the Bristol Aircraft Company for the carriage of persons of different circumferences At one end of this strop are four metal links, and a clip hook at the other end enables a loop to be made when passed around the chest of the rescued (see below)

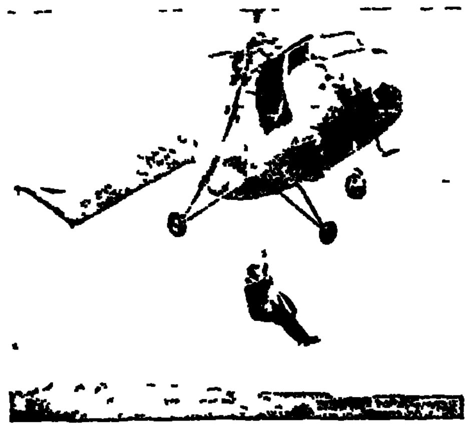

Fig 4—Bosun's chair in operation

(6) *A bosun's chair* made of stiff canvas and fitted with a quick-release mechanism (fig 4)

(7) *A winch*—This is a steel cable about 70 ft long, capable of carrying 400 lb The cable used during an operation is not usually more than 30–40 ft. long

(8) *A* SARAH *screen* for the reception of impulses from the small transmitting SARAH in the aircrews' "Mae West", thereby facilitating greatly the location of persons in the sea (SARAH=Search And Rescue And Homing)

(9) *Oxygen*—This is still the subject of experiments At present it consists of a 72-gallon oxygen bottle, with a Mk 7 valve fitted with a reducing valve and flow meter (fig 5), to be attached to the aircraft and lowered if required For immediate therapy the medical officer is also equipped with oxygen (see below)

Winching

Outside the aircraft on its starboard (right) side, just behind and above the entrance aperture, is the winch, by which the patient is lifted If the patient is capable of being lifted alone, a single strop like that designed by No 275 Squadron is lowered Right arm, head, and left arm are inserted into the loop in that order so that the strop passes round the back of the chest under the armpits, and then the toggle is drawn to the chest, thus securing the patient Should the patient be incapable or dead, the navigator, wearing an immersion suit (a strong rubberised suit with neck and wrist seals), is lowered in a bosun's chair He has a long "intercom" lead enabling him to keep in contact with the pilot, who operates the winch and can be informed of changes in position Attached to the winch hook is one end of the Bristol strop, the other end being passed round the patient by the navigator The hook is clipped to the appropriate link, and the signal to lift is given Having ascended to the aircraft the navigator disengages himself from the winch (quick-release box), attaches himself to the aircraft by the safety-belt, and swings the patient inboard

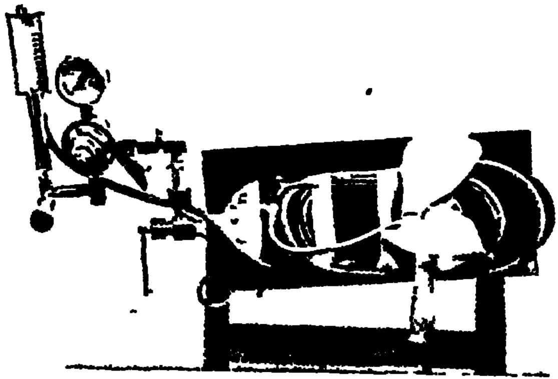

Fig 5—Oxygen bottle (72 gallons) with reducing valve and flow meter for lowering alone from helicopter

When the pilot is directly above the patient his view is obstructed by the fuselage of the aircraft, hence the necessity of the long "intercom" lead enabling the pilot to keep in contact with the navigator A two-mirror system has been fitted which enables the pilot to see the winching process, but, since the mirrors are convex, the object appears very small and it calls for further concentration by the pilot, who already has plenty to cope with

Practice at being winched, both dry and wet, is given to all aircrew, and the medical officer is also taught the modus operandi of the winch

The winching of a patient on a Neil Robertson stretcher is important This is a stretcher of narrow lathing supported by a backing of strong canvas (fig 2), in which the patient is strapped The stretcher is attached to a ring by four strands, the two attached to the head end are about 3 inches shorter than those attached to the tail end This means that the head is higher than the feet, a point which enables the winch operator (navigator) to catch a loop at the head and to pull the stretcher inboard As the stretcher ascends to the aircraft it acquires a slow spin from the motion of the rotor and from the natural torque Consequently an inexperienced navigator may misjudge the amount of spin, and the patient may be caught up against the bottom of the aircraft, causing further injury, but wherever it is possible, patients would be loaded into a grounded aircraft Another danger from spin is that the exhaust pipe from the engine is placed just below and to the rear of the entrance aperture and is apt to burn the patient's face and or feet as the stretcher gyrates For this reason a recent modification directs the exhaust gases backwards

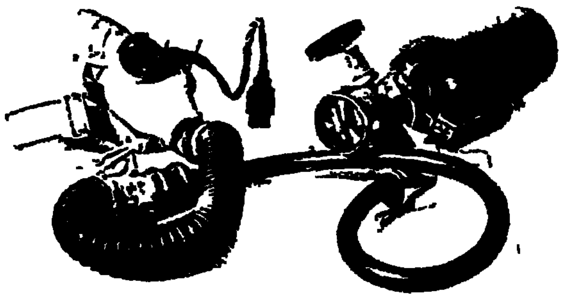

Fig 6—Ten minutes' supply of oxygen with aircrew oxygen mask, all carried by medical officer lowered from helicopter

Rapid spin on the end of the cable can be distressing if it continues for any length of time The partial answer to it is to look upwards at the aircraft

Winching from Dinghies

This operation is complicated by two factors (1) downdraught from the aircraft makes necessary a rapid run to the position to obviate blowing the dinghy out of position, and (2) in warm windless weather hovering is difficult owing to the low density of the air, making necessary extra power for a longer time The engine power of the Sycamore is such that hovering and lifting under such conditons may be impossible It must also be remembered that the pilot becomes more rapidly fatigued under these conditions

Other Observations on Winching

As the patient ascends, the helicopter is lowered to minimise any injury to the patient if the cable parts

In emergency the cable can be cut by releasing a spring-loaded cutter

Medical Officer's Equipment

Since the medical officer may be taken out in a helicopter and lowered on to a ship or to some otherwise inaccessible place, he must carry with him as much as possible in the way of equipment because a second drop of supplies may be impossible The equipment suggested is as follows

(1) *A standard bag containing the following articles*

(*a*) 540 ml of 6% 'Dextraven' in saline for transfusion

(*b*) Sterile giving set

(*c*) Sterile burn and wound dressings of various standard sizes, including " field " and " shell " dressings

(*d*) Extra unsterile bandage and gauze

(*e*) Tourniquet (St John's)

(*f*) Gooch splinting

(*g*) Antiseptic cream—dibromopropamidine (' Brulidine ')

(*h*) 2 sterile syringes (5 ml and 10 ml) and needles

(*i*) Ligatures in sterilised tubes

(*j*) Sutures on needles in sterilised tubes (intestinal and skin)

(*k*) 2 Spencer Wells artery forceps

(*l*) 1 pair of curved blunt Mayo scissors

(*m*) 1 Ryle's tube

(*n*) Ampoules for injection of adrenaline 1 1000, coramine 2 ml , calcium gluconate 10%, and water

(*o*) Four 'Tubunic ampoules of morphine gr $^{1}/_{4}$

(*p*) 20 ml of 2% procaine hydrochloride

(*q*) Ten vials of penicillin 500,000 units

(2) *Oxygen* —10 minutes' supply of oxygen can be carried with the medical officer This is put up in a small cylinder bearing a gauge reading in " Mins O_2 supply left " This can be given through the aircrew oxygen mask, and the advantage lies in the facts that the mask and oxygen linkage (fig 6) is standard throughout the Royal Air Force, and the mask is part of the medical officer's personal equipment

All the aforementioned equipment is carried on a strong webbing belt to which the bag is attached by a quick-release link, the oxygen bottle simply hooks on to the belt

(3) A standard " Mae West " incorporating a SARAH unit

The total weight of all this equipment is about 50 lb

Preparation of Landing-grounds Exercises

A suitable area is selected by previous reconnaissance, and at a later date the technique of removing a casualty by helicopter is demonstrated to hospital and ambulance staff A " patient " is set on the field of operation and a medical officer and a stretcher are lowered The " patient " is then put into the stretcher and winched into the aircraft, which lands at the hospital landing-site (the same area is used during an exercise) The waiting stretcher-party come forward and convey the " patient " to an ambulance and thence to hospital In Northern Ireland such landing-sites have been prepared at the Royal Victoria Hospital, Belfast, Cottage Hospital, Coleraine, British Military Hospital, Waringfield, and at H M S *Sea Eagle* at Londonderry, whence patients would be conveyed to Waterside Hospital A new hospital is being built at Londonderry, and it is proposed to include a landing-site in the hospital grounds Other sites are proposed at Enniskillen and Newry

Since only one Neil Robertson stretcher is carried by the aircraft, which may be required immediately for another emergency, it is hoped that hospitals will obtain Neil Robertson stretchers of their own, which could be exchanged for that in which the patient is delivered to hospital This would also prevent repeated movement of the casualty and reduce shock

Close liaison is also maintained with the coastguards, and two exercises consisting in lowering a medical officer into and removing a " patient " from a lifeboat at sea have been carried out successfully by the flight to which I am attached The main difficulties with regard to removing an injured person from a lifeboat are lack of space both inside the vessel and outside for the easy management of a patient, and the constant pronounced motion of a small vessel even in calm weather

Approach to a Grounded Helicopter with Engine Running

The dangers of approaching a helicopter whose rotors are revolving cannot be emphasised too often It must be remembered that there are two rotors, the more dangerous being the small vertical tail rotor, which by virtue of its speed is difficult to see Before approaching, either obtain the pilot's permission (he sits on the right-hand side facing forward just in front of the patient's entrance) by catching his eye and waiting for the thumbs up sign or, better still, wait till the rotors stop turning When the all clear is given, move directly to the patient's entrance All approach from the rear is strictly forbidden because it is dangerous

Thanks are due to Flight-Lieutenant A G A Mitchell, Officer Commanding ' F ' Flight, No 275 Search and Rescue Helicopter Squadron, and to both air and ground crew for their full and ready cooperation, and to the coastguards, lifeboat men, ambulance teams, and hospitals with whom we have been associated The photographic section of the station are thanked for both the excellence of their work and their kindly tolerance The photographs are reproduced here by permission of the Air Ministry, and the Crown copyright is reserved

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JOINT CONSULTANTS COMMITTEE

THE committee met on Jan 29 with SIR RUSSELL BRAIN in the chair

Consideration was given to the preparation of further evidence in reply to questions raised by the Royal Commission at its hearing on Dec 18 Representatives of senior administrative medical officers of regional hospital boards attended the meeting and discussed with the committee the evidence to be put before the Royal Commission on behalf of administrative medical staff, whose remuneration hitherto has been related to that of hospital clinical staff Reference was made to the fact that regional psychiatrists are remunerated for their administrative duties at a rate substantially lower than that of a consultant—a situation which discourages psychiatrists of consultant calibre from applying for, or remaining in, these appointments It was reported that in Scotland, and in some regions in England, there is no post of regional psychiatrist, the boards obtaining the necessary advice through individual consultant advisers and through specialist advisory committees In these circumstances the consultant adviser suffers no diminution of his consultant salary in respect of his advisory duties This has been the normal method by which boards have obtained expert advice in specialties other than psychiatry, and in the view of the Joint Consultants Committee it has operated satisfactorily

It was reported that, following further discussions on hospital medical staffing, the Ministry had undertaken to consider detailed suggestions put forward by the Joint Consultants Committee for carrying out a review of consultant establishments The committee reaffirmed its conviction that it would be unrealistic to consider any long-term changes in the pattern of hospital staffing below the consultant level until there was more information—such as would be revealed by a review—of the needs of hospitals, and particularly of the volume of clinical work requiring consultants for its proper performance Pending the outcome of such a survey the committee had proposed to the Ministry that steps should be taken to give a greater measure of security, and an increase in remuneration, to "time-expired" senior registrars

The committee had before it for comment draft memoranda prepared by the Ministries of Health and Education upon the child-guidance service A report was also submitted regarding the criticisms which had been levelled against the memoranda by the Royal Medico-Psychological Association and the Psychological Medicine Group Committee of the British Medical Association, mainly on the ground that the proposals for the development of the child-guidance service appeared to be directed towards the educational rather than the medical needs of the service The committee supported this general criticism of the draft memoranda, and is preparing a statement of its views for consideration by the Ministry of Health

The committee considered a suggestion that when the Ministry issues a circular to hospital authorities containing advice on clinical matters the name of the actual author or authors should be disclosed It appeared to the committee, however, that it was of even greater importance to know what might be the implications of such Ministerial "directives" in the event of a legal action involving a member of a hospital medical staff, and the committee decided to seek advice on this point

Other matters discussed included the future of venereology, medical advisory machinery in mental hospitals, the completion of cremation certificates, and the provision of anæsthetic assistance in mental hospitals by medical staff untrained in anæsthesia

The committee decided to arrange a conference with representatives of hospital provident schemes and other interested bodies for an exchange of views and information on private bed charges and related questions

The present membership of the Joint Consultants Committee is

Sir Russell Brain (chairman), Sir Harold Boldero and Prof Robert Platt (appointed by the Royal College of Physicians), Sir James Paterson Ross, Mr Lawrence Abel, and Prof I Aird (appointed by the Royal College of Surgeons), Prof Andrew Claye and Mr I Jackson (appointed by the Royal College of Obstetricians and Gynæcologists), Dr A Rae Gilchrist (appointed by the Royal College of Physicians of Edinburgh), Prof J Bruce (appointed by the Royal College of Surgeons of Edinburgh), Mr W W Galbraith (appointed by the Royal Faculty of Physicians and Surgeons of Glasgow), and Dr J D S Cameron, Prof P C P Cloake, Dr T Rowland Hill, Mr J R Nicholson-Lailey, Mr T Holmes Sellors, and Prof G I Strachan (appointed by the Central Consultants and Specialists Committee of the British Medical Association)

The Widdicombe File

XLIII MRS WORTHINGTON

My Dear Nephew Richard,

About the time you first started throwing your rattle out of the pram, I used to tease your mother by crooning the current Noel Coward ditty "Don't put your daughter on the stage, Mrs Worthington, don't put your daughter on the stage!" But it made no difference to my hope that you might be headed off from playing the drama and comedy of Medicine You have made your entrance you are on your own

Perhaps your embittered embryo-consultant friends who fled to farming or Zanzibar were miscast for Medicine The pity is that the farmer did not earlier search his heart to look behind the seed to the soil itself, that the coloniser did not lift his roots much sooner The joy is that they did before the end Surely what really matters is to find an acceptable way of life, a way of thought, a Faith, and maybe grace

Really I have no qualms about either your soul or your choice of psychiatry I pin my hope on your significant little sentence "It's a stimulating line and often very rewarding in many ways" You are aware of the stimulus it is getting stronger it evokes a response the response pleases you the pleasure is the bitter-sweet of adult life

Now you are immersed in your chosen specialty, of course the field looks bigger than you thought But aren't you looking at it through the oil-immersion lens, the window to more and more of less and less ? I am always fascinated by the absorption of the specialist in selected tissues—the starlight twinkle from the convex mirror of the cornea, the rapture of Sappho reflected from the cervical erosion I too have tasted such joy Oto- was full of all the fun of what the butler saw, rhino- was a skittle-alley of destructive invitation, laryngology was a breath-taking helterskelter of bouncing bronchoscopes over cord and carina An E N T outpatient session was becoming more attractive to me than 2*s* 4*d* worth of the back row at the cinema Then one day the clip on the dark-room windowsill went wrong the blind flew up Through the cyclops hole in my forehead-mirror I saw with a surging heart that the sky was blue, the sun so bright, the horizon so far away A butterfly perched on the window Psyche was tugging at the tapes of my overall gown Psyche won But somebody must stay in the strait-jacket to specialise All honour to you, Richard This is your life

But your life and mine are what we make them Mrs Worthington had made hers She had gone on to the more unselfish question of what to do with her daughter You and I may have to face a similar problem *Should we discourage our own sons and daughters from a medical career ?*

Please note that I use the word discourage If our children have really set their hearts on doing Medicine, you or I will not be able to stop them, any more than if they are set on becoming saggermakers'-bottom-knockers or any other bizarre occupation that takes their fancy from watching "What's my Line" on television We shall have to fork out the fees and look cheerful about it, just as we shall have to reconcile ourselves to their choice of marriage partners

The sound of wedding bells switches my mind straight back to Mrs Worthington's daughter and our own ewe-lambs Is it worth it for women to take up Medicine ? Do you think that a girl with a strong sense of vocation to heal the sick is wise to go the whole way ? Wouldn't she do better to be a nurse ? Women are so intense about such things, and tension is hardly the secret of walking the tightrope to the Medical Register And what is their fate at the end of the course ? First the glorious dedicated virginity of Femme Sole I pass The alternative is marriage, but to whom? Two doctors of opposite sex talk to each other if they talk medical shop, the poor girl can forget the golden ring if they don't talk shop she can forget Medicine A psychosomatic choice, just as simple as that To practise or not to practise, that is the question for Eros to torture Psyche with in a medical union If she marries into the laity she will find few Englishmen willing to admit the superiority of their wives even in knowledge of the internal-combustion engine, let alone physiology And quite right too Until we have become even more conditioned by films and television to American matriarchy, I hope we shall resist the transatlantic view that a man is just something handy to have around the house We shall chain ourselves to the Palace railings before that

It always seems to be very different for boys They are not so intense In fact an effort is often needed to bring their minds to bear on the sordid subject of separation from the first-stage rocket of father's payroll They may have a vague idea whether their interest lies in Things or People or Ideas, but their motives for choosing a career often seem quite fortuitous Not so the motives of their parents You and I, Richard, we must be quite unscrupulous If we really want to head our sons away from Medicine we must start their indoctrination at the toddler stage I contemplate forcing them into high chairs at every meeting of the B M A and our Local Medical Committee Steady propaganda right up to puberty should shatter every fairytale of Æsculapius Then do you know what will happen? The contrary ingrates will choose to take up Medicine out of sheer cussedness or some inner call

If you prefer it, you can work the other way round Teach him to mewl Ninety-nine, to measure out his calories, to doodle on E C 10 Get his I Q done before his vaccination Make it a feature of childhood games to be for ever chasing his mental age Let him toddle through the door of the nursery-school with a Purpose, to keep his orthoptic exercises focused on Eleven Plus Furtively ransack the bookshops for every published test paper Cultivate smart-Alec repartee *Q* Why do the swallows fly to Africa in winter? *A* Because it's too far to walk That's the stuff to wean young England from " guess-I-cawn't figure it out, gee, let's get outa here, bang, bang!" The Eleven Plus will stand him in good stead in a busy outpatient session some day, or maybe help him climbing ladders

All right then, we have dragged, pushed, bullied, coaxed, and cheated young Gold Cane over the State's first hurdle He has a brand mark tattooed on his buttock *I am a Grammar-school type* Then he is separated from the goats and sent to the dipping-tank for brainwashing and reindoctrination towards an academic life If he is one of the fortunate ones he may graze transiently on a few mouthfuls of Arts and Classics as he is goaded towards the gate marked Science Specialisation starts at 13 or 14, with a tribal initiation before the altar of Technology, a shadow dance for 1st M B We dedicate our youth before their minds mature This is the New Britain

On sweep the chosen through the face-saving farce of Ordinary Level G C E to the privileged kudos of the VIth form and the intellectual climax of Advanced Level It seems a pity that the curriculum has to be so cramped, but otherwise there would never be time to fill in all the university application forms without half a term devoted to administration The Headmaster of Eton recently compared university selection procedure to the chances of parking a car in Central London, his sentiment was echoed by an eminent Vice-Chancellor as deplorable chaos Because no-one can find a remedy, you and I, Richard, must enter our sons for three or four universities in the hope that the ball in the roulette wheel of one of them will stop against our cherished human stake We must wade through calendars, and faculty prospectuses, and guides to medical degrees, we must fill in multipage application forms in duplicate, wave birth certificates, G C E s, exemptions, testimonials, and references We must dash to the four quarters of the Realm for interviews, fill in forms for digs and halls of residence, leave ducats on deposit All knowing full well that one child can take up only one place Talk about Bull in the services? It is knee-deep in the quadrangles of Britain

When all the right forms have been filled in, and the Mad Hatter's September teaparty has picked its winners, the old old question pops up, who is going to pay? Something like 80% of undergraduates are grant-aided either by the State or local authorities, so you and I will naturally want to jump on the bandwagon as it runs by All we are likely to get is a push in the face, and we shall be back in the gutter The means test is a cunning device of the Devil to break family tradition in Medicine it means a generation in shirt-sleeves to win back grandpa's rubber gloves

And at the end of it all? Consultant practice, with no holds barred? Or general practice? If so, by the time they qualify, will the public be licked into M I Room parade submission, or will doctors still be contemptuously called by their bare surnames, summoned and paid with less respect than the plumber? Will they choose their wives to be qualified working partners, nurses for ancillary help, or merely decorative to answer the phone? Will their sense of vocation sustain them through all the petty irritations of the N H S ? Let us pray so, for their sakes, and for the sake of England

Will they choose preventive medicine, that queer mixture of political shuttlecocks and visionaries? If so, will they dabble in the tug-of-war over the curative personal services, potter in the no-man's-land of education, or strike out boldly like the 19th-century cohorts of forthright men? And will they do it for less money than their professional colleagues in other fields? One minute's silence in the Town Council on their passing seems a poor reward

Will they follow one of the less-trodden paths of Medicine—the Services, the missions, industrial practice, Government office, down to the sea in ships, paramedical research, even journalism?

Richard, my boy, thank your stars that you are in But think twice about whom you bring in with you Mrs Worthington was wise to seek advice, don't you think? Excuse me now, I must hurry to chain myself to the Palace railings and call for policewomen protection Mrs Worthington's daughter is leading a charge down The Mall of the most delicious medically qualified lovelies you ever saw *Moriturus te saluto*

Your affectionate Uncle,
TOM COBBLEIGH

In England Now

A Running Commentary by Peripatetic Correspondents

In this American town the ambulance with the most urgent note to its siren bears the inscription "Dog Ambulance", and it can often be seen making, at breakneck speed, for the imposing "City Hospital for Sick Animals (Inc.)." According to our professor, whose dog once had its ears syringed there, the administrative efficiency of this institution might well be the envy of all the human hospitals. There is a comprehensive appointment system for all but acute emergencies, and patients are not kept hanging about in the waiting-hall. The house-officers wear name badges to facilitate rapport and lose no time in assigning Pluto to a ward—e.g., M.D.S., meaning male dog surgical—which is light and airy and has ample space between baskets. Special investigations, including blood chemistry and electrocardiography, are done by laboratories with a 24-hour service. Thus a cat in F.C.M. began a diet of milk and fish on the day that a barium meal showed a duodenal ulcer.

There are three full-time psychiatrists on the staff, one with special training in psychoanalytic methods, while another has made a special study of the problems encountered in little dogs. Visiting hours are generous but nevertheless many patients require sedation. An attempt to avoid hospitalisation is reflected in the new outpatient department which is open day and night for emergencies, and accommodates many special clinics, as well as those for routine diagnosis and treatment. The allergy clinic is one of the most interesting, long courses of desensitising injections being given for various offending allergens, including human hair. A notable feature of the new building is the width of its entrance, because, it is rumoured, some years ago a circus elephant was rushed in with a suspected intussusception. Although so rare an exigency is unlikely to recur, a wide front door has proved its worth for the occasional cow admitted for her confinement.

* * *

I rashly informed my patient with a rare disease that I would attend a clinical meeting on the subject and afterwards give her all the latest information. Now I have been to the meeting I have an uneasy feeling that my explanation must run as follows:

> "You have had this disease for some time and it does you no harm. You have had one small test and you take brown tablets *x*. Now it has been discovered that the disease can be diagnosed earlier by a multitude of tests, and can then be prevented. The way to prevent it is to take brown tablets *x*."

* * *

Though a fairly regular peripatetic correspondent, I have had only two repercussions from my contributions. I recently stated that Lord Davidson of Lambeth was the only archbishop who retired. This error has been brought home to me by a colleague who reminds me that Cosmo Gordon Lang retired in 1942 and was granted a peerage. The second repercussion was more fruitful. I wrote one May that the blossom of quince-trees was coming out in crops like chickenpox and the quantity heralded a bumper crop. A lady doctor, through the good offices of the Editor, got in touch with me and offered to make me quince jam, she providing the sugar and I the quinces. In due course this was done, we sharing some twenty pounds, which was appreciated particularly by the older generation.

* * *

Our sanatorium has a geriatric unit, and in it we have a lady with mitral stenosis who has survived a saddle embolus. Both her legs have been amputated at the level of the knee-joint. She had her moment of triumph last week. "Tha'll have a job, lad!" she said, when the chiropodist offered to cut her toenails for her.

* * *

Lately I had to propose the health of The Lasses at a well-attended Burns supper for diabetics. I did not realise until a Lass made a speech in reply how exceedingly complimentary I should have been. She firmly thanked me for all the kind things I should have said, but didn't.

* * *

The problem of chaperonage has always seemed to me to be a simple matter dependent on the magnitude of the expedition and the experience of those taking part. My six-year-old son accompanies his younger sister to the local shops but is taken to town by his twelve-year-old sister. She now has a French friend staying with her and they will soon both be escorted to France by my elder son, who at fifteen is an experienced traveller and a reliable chaperon. No sooner were the arrangements for this journey complete, however, than I received a letter from a rich American acquaintance, imploring me to find a chaperon to take her daughter to France, all expenses paid. At first the solution seemed obvious. The American girl (aged seventeen) could join the party in charge of my son (aged fifteen), who would thereby get his fare paid. Something tells me, however, that this idea is unsound. Obviously there is more in this business of chaperonage than meets the eye, and I shall probably end by finding a locum and enjoying a free trip to France myself.

* * *

HAZARDS OF SEMINAL ELECTROPHORESIS

The turning of worms
Is conducted on terms
Which have little to do with
 the movement of sperms.

But recently Schröder,[1]
And others absurder,
Have suggested a method
 of racial murder.

We are grateful to Lewin[2]
Whose work is not new in
This field, for informing us
 what chaps are doin'.

I see from his thesis
Electrophoresis
Might have an effect to
 which one of the keys is.

With skilled A.I.D.
And the current D.C.
We determine which sperm
 brings a he or a she.

It's some comfort that Kordts[3]
Has a series of noughts
On his records when trying to
 check these reports.

And his colleague A. Pilz[4]
Finds his work hardly fills
All the postulates needed
 to cancel Kordts' "nils."

The hotter the buffer
Solution, the rougher
The sperms fare, but that doesn't
 make the child tougher.

Though the odds on a Mong-
Ol are not very long,
It *would* be a damn' silly way to
 go wrong.

And as for a spastic
Well, that's not fantastic
Though we know that statistics are
 pretty elastic.

What with fœtal anomalies
And episcopal homilies[5]
It seems it were wise to forego
 A.1 families.

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[1] Schröder, V. N. *Z. Tierz. ZüchtBiol.* 1941, 50, 1.
[2] Lewin, S. *Lancet*, Feb. 8, 1958, p. 323.
[3] Kordts, E. *Z. Tierz. ZüchtBiol.* 1952, 60, 221.
[4] Pilz, A. *ibid.* p. 315.
[5] Cantuar, Geoffrey. *Proc. Ch. Cong.* 1957.

Letters to the Editor

STAPHYLOCOCCAL DISEASE

SIR,—Your editorial of Feb 1 refers particularly to staphylococcal infections in infancy, but it serves to focus attention on the subject as a whole

That serious staphylococcal disease is on the increase is evident and it can be classified under four main headings

Group I Primary invasive infections due to *Staphylococcus aureus*

Group II Serious staphylococcal infections accompanying other infections

Group III Superimposed staphylococcal infections in the wake of wide-spectrum antibiotics

Group IV Serious infections in which the *Staph albus* (coagulase-negative) is the only organism recoverable from the patient

Group I

A striking rise in the incidence of invasive disease due to the *Staph aureus* has occurred in the past four years in Leeds and surrounding districts Over 100 of these seriously ill patients of all age-groups have been investigated at Seacroft Hospital, Leeds The clinical pattern of this disease was fairly constant for different age-groups In infancy severe gastroenteritis, sometimes with purpuric rash and associated pneumonia, was a common picture 4 in the series developed acute suprarenal failure of the Waterhouse-Friderichsen type, and the same number developed acute exfoliative dermatitis with associated pemphigus Others presented a pneumonic picture only In toddlers lung abscess was common

In older children initial pyrexia of uncertain origin, often with prostration, was quickly followed by one or more septic metastatic lesions, such as cerebral abscess with meningitis, osteomyelitis or periostitis, septic pericarditis, or embolic gangrene of fingers or toes Most of these had associated metastatic multiple lung abscesses Some developed acute enteritis, often prolonged, resembling acute ulcerative colitis In one adult who died, a triple heart lesion was present—acute inflammation of the cusps of the mitral valve, fresh myocardial infarction of septic embolic nature, and acute septic pericarditis

Late cases tended to respond slowly or not at all to treatment Death, which occurred in about 10% of all cases, was sometimes due to acute hæmorrhage from severe ulceration of the colon, while others died of anuria following septic pyelonephritis 50% of all Waterhouse-Friderichsen cases died in spite of supplementary hormone therapy

None of the patients in this group had been in hospital in the recent past, nor had any had contact with recently discharged patients, and their in-vitro sensitivity patterns bore no resemblance to those of the common offending hospital staphylococci

Group II

These were serious mixed infections, in which staphylococcal disease was present on admission in association with other specific infections These included meningococcal meningitis, tuberculous meningitis, and 2 cases of poliomyelitis In fatal salmonellosis of the older age-groups, associated staphylococcal general infection was the apparent cause of death in 4 cases

Group III

The infections in this group, which followed in the wake of wide-spectrum antibiotics, do not require description These superimposed infections can largely be prevented by cubicle-nursing technique, the use of combined antibiotics, and the avoidance of oral antibiotics in the presence of skin sepsis With these measures they can be eliminated from hospital practice

Group IV

A smaller number of severe invasive infections, similar in every respect to those in group I, have been admitted to this hospital, but in these the *Staph albus* (coagulase-negative) was the only organism recovered from the patient Whether these were causative organisms or contaminants cannot yet be established

These groups of clinical entities represent to our mind the main staphylococcal problem at present Increased virulence and invasiveness of the staphylococcus appear to lie behind this changing pattern Those awake to the menace can do much to save lives by immediate investigation and vigorous treatment of suspected cases

Seacroft Hospital
Leeds

E C BENN
E F MURPHY

SEPTIC SURGERY

SIR,—I was interested to read Dr Gray's letter in your issue of Feb 22 It reveals a narrow viewpoint and an ignorance of the real practice of his surgical colleagues

He states "It is very much against the interest of the patient for surgeons to leave the theatre to visit a ward or casualty to see an urgent admission whilst wearing theatre robes" This statement gives a false picture When such visits are imperative, the surgeon, after removing cap, mask, and theatre footwear, *dons a special robe which is* discarded before entry into the theatre It is *not* a garment worn *in* the theatre Such visits are usually urgent and are in the best interests of the patient—indeed they may be lifesaving

Most surgeons have a real appreciation of the incidence of bacterial infection during operative procedures They are also aware of the greater risk of cross-infection in surgical wards Many of us have striven for years to combat these by precept and example, but I agree there is still much to do

The idea of separate days for elective and emergency lists has little to commend it There is insufficient staff and an inadequate number of theatres to undertake it Moreover, there are not sufficient days in the week to operate the suggestion

London, W 1

ILLTYD JAMES

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—As nobody more eminent has seen fit to question the validity of Dr Clyne's article of Feb 1, may I make some comments?

It is a pity that his capacity for doubt, allowed free play where his motives are concerned, is given so little scope when it comes to interpretation There seems little reason to suppose that the ruminations reported in his article have contributed significantly to his patients' welfare and I do not believe that scientific detachment is so hard to achieve in the handling of physical complaints as he seems to imply Nor can I see any reason to accept his assertion that the three Furies, Anxiety, Hostility, and Guilt, hold undisputed sway over our actions Facts, based on observation and experience, can guide our actions irrespective of our personalities in many fields of medicine

Of course it is true that in the personal relationship, such as that existing between patient and doctor, personalities must play some part In psychotherapy—and most medicine contains an *element of psychotherapy*—the doctor's personality plays a very important part and thus should be understood, but is this a new discovery? Does it deserve the prominence which is now so fashionable?

The tendency to make the central aim of training doctors for psychotherapy the achievement of a personality change in the doctor seems to be getting rather out of hand, so that the analysis of the doctor is taking precedence over the description and investigation of the disease Dr Clyne's application of this approach to a child with a physical complaint serves to underline its basic anti-scientific character

London, N W 5 ANTHONY RYLE

DERMATITIS CAUSED BY PENICILLIN IN MILK

SIR,—The article by Dr Vickers and his colleagues (Feb 15) is timely In this dairying part of the agricultural world, cheesemakers have difficulty in initiating the process of cheesemaking when penicillin is present in the milk in a concentration of over 0 03 units per ml In bulked milk of 1000 gallons or more penicillin is found about once a week, but in a concentration of usually less than 1 unit per ml However, on one occasion recently 10 units per ml was found in 750 gallons of milk As this included 150 gallons from one recently treated herd it can be assumed that there is a theoretical possibility of obtaining up to 50 units of penicillin in such milk, if sold unbulked to consumers

It should be noted that people living in small country towns and villages invariably drink unbulked milk It is, perhaps, a doubtful privilege

Crewkerne Somerset L E WEAR

FULMINATING BERIBERI

SIR,—Dr Baron and Mr Oliver (Feb 15) point out the rarity of deaths from beriberi in Britain, and could not find a previous report of a case here showing "all five possible manifestations of aneurine deficiency" The following case-report may be of interest

An ex-seaman, aged 49, was admitted to St Bartholomew's Hospital on Jan 11, 1956, complaining of a swollen scrotum He preferred beer to food, and he could not give a coherent history He could not move his eyes laterally the attempt produced nystagmus and diplopia Tendon reflexes were not obtained in the legs, there was a right Babinski response There was gross œdema up to his waist, ascites, ballooning of the genitalia, tachycardia, and a slightly raised jugular venous pressure, the blood-pressure was 160/85 mm Hg There were moist sounds at the bases of both lungs, and diffuse expiratory rhonchi His lips, tongue, and scrotum showed erythema, desquamation, and moist fissures The urine contained excess urobilin Liver-function tests gave normal results A chest radiograph showed that the heart was enlarged

He was treated with digoxin, mersalyl, penicillin, 'Parentrovite', and an intravenous preparation of the vitamin-B complex with ascorbic acid Two days later he could look laterally, but his mental state was worse The heart-rate decreased, but there was no rapid diuresis Acupuncture produced 12 litres of fluid, which allowed the detection of an enlarged liver, and deflated the genitalia In the third week the only tendon reflex obtained was from the left biceps, both plantar responses were flexor, there was myotatic irritability of the left calf, and diminished sensation in the legs After ten weeks there was little improvement in his mental or neurological state, but he was otherwise well He was transferred voluntarily to a mental hospital, which he left the next day

It seems that this man, too, had beriberi with all its possible manifestations This additional case suggests that even severe beriberi may not be so rare in Britain as might be supposed from the scarcity of deaths and published reports

St Bartholomew's Hospital,
London, E C 1

G C R MORRIS

FŒTAL LOSS IN PREGNANCY TOXÆMIA

SIR,—Mr FitzGerald and Dr Clift (Feb 8) in their valuable paper have drawn attention to some important aspects of the loss of fœtal life in cases of toxæmia and hypertension Whereas the general fœtal risk in these diseases has been recognised for many years it is only recently that attempts such as theirs have been made to separate more clearly the different types of case and their particular risks one from another The two main types comprise those showing placental separation (accidental hæmorrhage) and those in which the placenta becomes progressively more and more infarcted until it can no longer sustain fœtal life In both, the fœtus is in danger and it is for the obstetrician to decide how great this danger may be and what should be done about it

Accidental hæmorrhage by its very nature commands attention, and the more severe the bleeding or the more severe the signs of concealed hæmorrhage the more attention is likely to be paid to it slight hæmorrhage also must not be neglected, for it is a serious warning Slowly developing *placental infarction* presents in a different, though just as characteristic, way The size of the uterus and contents are much less than one would expect from the duration of amenorrhœa, and one's tentative diagnosis may be "wrong dates", but herein lies a great danger, for if placental insufficiency is misdiagnosed as wrong dates intrauterine death may occur As Mr FitzGerald and Dr Clift point out, another important feature of this type of case is the failure of the fœtus to grow, but this can be most difficult to recognise and may give little indication of the seriousness of the lesion and the need for urgent treatment In such cases, and to a lesser extent in accidental hæmorrhage, we have found [1] the urinary excretion of pregnanediol in a 24-hour specimen to be helpful One case will illustrate this matter

A primigravida, aged 20, with very slight hypertension (one might almost say insignificant) was observed to have a pregnancy whose size was quite out of keeping with the period of amenorrhœa, thus, in the 35th week of amenorrhœa the uterus just extended to the umbilicus and the estimated size of the fœtus was about 2 lb Gross placental insufficiency was diagnosed, which was supported by a pregnanediol excretion on two occasions of 8 and 6 mg per 24 hours (normal range for 35 weeks approximately 25–70 mg per 24 hours) Intrauterine fœtal death was thought to be inevitable within a few days, so even though the prospects of getting a viable child were slight cæsarean section was advised At operation, a fœtus weighing 2 lb 2 oz was delivered, the placenta, which was 11 cm (4½ in) across, weighed 5 oz, and as more than half of it appeared infarcted it is remarkable that the fœtus had survived as long as it did The mother made a good recovery, and we are glad to report that now, 5 weeks after operation, the child weighs 2 lb 15 oz and thrives

The pregnanediol excretion therefore confirmed our diagnosis and underlined the urgent need for treatment Cæsarean section was chosen as being in the best interests of mother and child [2]

Department of Obstetrics and
Gynæcology University of Sheffield
Jessop Hospital for Women,
Sheffield

C S RUSSELL
C J DEWHURST

SIR,—Having read the article by Mr FitzGerald and Dr Clift and an earlier one by FitzGerald and McFarlane,[3] I should like to make two comments

In the earlier article, it is stated that the standard for

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1 Russell, C S Paine C G Coyle, M G, Dewhurst C J *J Obstet Gynec, Brit Emp* 1957 64 649
2 Dewhurst C J *ibid* 1955 62, 706
3 FitzGerald, T B, McFarlane, C N *Brit med J* 1955, ii, 358

toxæmia “ has been a blood-pressure of 150/100 or more with or without albuminuria ”, and that “ toxæmia cases show an incidence [of fœtal distress] of 8 4% compared with 6 7% in the non-toxæmic group It is surprising that this difference is not more pronounced ” With due respect, however, I would point out that Prof F J Browne drew the line at 130/70 and he is backed by all physiological investigators on this point I, too, have found that 90% of 1600 women are below this figure on booking Were Mr FitzGerald to accept the Browne standard, he would find less surprising results

Secondly, we read in the recent article “ the baby ‘ fades out ’ without any clearcut exacerbation of the toxæmia ”; and later, “ Examination of case-records does not reveal any consistent signs of worsening of the toxæmia ” This, I submit, should not cause any surprise Sophian and Franklin have clearly shown that resistance to uterine stretching causes renal ischæmia leading to hypertension, proteinuria, and œdema The amelioration in the mother’s condition is brought about by an easing of the intrauterine tension This presages the death of the fœtus

My indications for interrupting a pregnancy are

(1) Sudden exacerbation of the cardinal signs foreshadowing antepartum hæmorrhage

(2) Gradual improvement of the cardinal signs meaning death of the fœtus within a few days

(3) The presence of albuminuria (stationary or slowly mounting in quantity) for 3 weeks

All these are irrespective of the stage of pregnancy

The perinatal mortality at this hospital for the past 8 years has been 3 73% in 2700 cases of either hypertension or pre-eclampsia

British Hospital for Mothers and Babies,
London, S E 18
C K VARTAN

ANÆSTHESIA FOR FORCEPS DELIVERY

SIR,—Regarding the methods used and the results obtained, may I amplify the statements by Dr Hamer Hodges and his colleagues (Jan 11) about the technique described in my letter of Dec 14

Of the 8 patients, all but the first 2 did indeed receive local infiltration of the proposed site of episiotomy This is part of the routine technique as it has so far been evolved, as I have described it elsewhere, and as it is being practised in other centres 2 patients received supplementary cyclopropane in 1 the method was a failure as far as the mother was concerned since pain was still appreciated, in the other, the mother had become unmanageable in her “ semi-drunken state ” Another patient required a few breaths of N_2O/O_2 mixture during the insertion of deep sutures in the episiotomy wound following delivery

Of the 8 infants, 4 were breathing well within 30 seconds, and 1 within 1 minute of delivery, the 2 whose mothers received cyclopropane supplementation were slower to respond (to 1 of these levallorphan was given and satisfactory breathing and crying followed immediately) The 8th child referred to emerged in a rather depressed state after a difficult delivery involving a reapplication of the forceps after a repeat rotation from the transverse position The child gasped on delivery and much meconium-stained liquor was aspirated from its upper respiratory tract, it gave its first full-throated cry at 7 minutes This case incidentally was a tribute to the method, 2 minutes after the episiotomy was sutured, the mother was “ talking intelligently and was delighted and surprised to learn that she had a son ”, the following day she said that she had no memory of the events of operation

No-one has yet claimed to have worked out a scheme for routine use—we are still, as I have said before, groping Certainly I would include the prophylactic use of levallorphan in any subsequent modification, and I feel that infiltration of the skin along the episiotomy line is an advantage Those doctors and midwives who watched the conduct of my small series were very favourably impressed by the promise (not the polished and final perfection) of the technique Dr Hamer Hodges and his colleagues unfortunately did not observe the conduct of any of the cases

I included Mr J G O’Sullivan’s name in my letter of Dec 14 in a spirit of honest credit-giving, for it was he who gave me to think on the subject initially, and we worked together on the details and modifications As senior obstetric registrar, he naturally did not personally conduct all the deliveries, but he was present during most of them

Dr Hamer Hodges and his colleagues ask why I “ did not use the technique on any of the numerous occasions available to (me) during the whole of the last five months of (my) appointment ” In fact, for various reasons, only 10 opportunities presented themselves to me for anæsthesia for a forceps delivery during this period Of these, only 2 fell into the “ chlorpromazine accepted ” class (that is, they were being conducted by an obstetric firm which permitted the use of chlorpromazine during labour) and did not, at the same time, evidence disturbing fœtal distress (I am not prepared to subject the latter group to this method until I am certain that I will cause no harm) The final 2 were delivered when Mr O’Sullivan happened not be be on the premises, and, as I have said, we did try to make this a combined effort

Mercy Hospital,
Pittsburgh, Pennsylvania
J SELWYN CRAWFORD

ANTIBIOTIC PROPHYLAXIS

SIR,—Dr Warren Crowe (Jan 18) and Dr Sklar (Feb 1) have in many ways expressed what I feel about the use of sulphonamides and antibiotics I, too, have been using sulphaethylthiadiazole (‘ Sethadil ’) and on the whole agee with Dr Sklar Dr Jhaveri (Feb 1) asks if sulphonamides in effective doses are not more toxic and hazardous than penicillin—but this does not apply when there is a sulphonamide which has little or no toxic effects

Penicillin is the antibiotic of choice in respiratory infections, but there is always the danger of sensitivity and this has made one cautious in its use I have often prescribed sethadil and there has been no evidence of any side-effects The absence of complications when using this sulphonamide prophylactically or therapeutically has therefore been established in my experience

Hove, Sussex
M L PLATT

TECHNIQUE OF INTRA-ARTICULAR INJECTION

SIR,—Mr Grant Waugh (Dec 28) and Mr Kaplan (Feb 15) have described methods of minimising the pain of intra-articular injections Some practitioners who have not previously attempted such injections may be prompted, by these communications, to use them to treat arthritic joints It therefore seems worth drawing attention to one factor which often determines the amount of pain caused, and which has not been mentioned by either of your correspondents, though I have no doubt they are well aware of it

The ease or difficulty with which puncture of a joint is effected largely depends on the state of its capsule Distended joints are easy to enter stiff contracted ones can be very difficult, and the attempt may cause severe pain Whilst it is possible, with a little experience, to inject the latter if even a small joint space still exists, I have usually found that the treatment—apart altogether from the initial pain it caused—afforded the patient very little relief in such cases

This is not surprising Hydrocortisone acts by modifying an inflammatory, exudative response,[1] and neither it, nor lactic acid, can be expected to influence symptoms associated with capsular fibrosis, gross attrition of articular surfaces, and a deficit of synovial fluid

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[1] Glyn J H Cortisone Therapy, p 85 London, 1957

To the points made by your correspondents then, I would add this If the operator, using the correct needles and an appropriate technique, finds that in a given case, attempts at intra-articular injection are painful or difficult, he would do well to consider whether such injections are, in fact, a logical treatment for the particular patient concerned

Royal Free Hospital,
London, W C 1

RICHARD HARRISON

EPILEPSY AND HYSTERIA

SIR,—Your leader of Feb 15 illustrates the quandary about the precise differentiation between epilepsy and hysteria, and the status of the concept of hystero-epilepsy for borderline cases You note that "formal psychotherapy may very occasionally have a dramatic effect on epilepsy", and you conclude "It seems we must reconsider the concept of hystero-epilepsy as a more fundamental problem in the physical and mental genesis of epilepsy"

I was fortunate some years ago to have a patient with hystero-epilepsy submit himself for formal analytic psychotherapy, after a long and difficult analysis there was indeed a dramatic abreaction and a complete (and permanent) cure The case was published[1] largely because of certain points in technique But a consideration of the psychopathology and clinical features, when compared with that of other similar cases in the literature, led me to the conclusion that "epilepsy and hysteria are extreme ends of a continuous series with an intermediate connecting group known as hystero-epilepsy"

A psychological approach is seldom attempted in these cases, and I would be interested to hear of other successes (or otherwise) of analytic therapy

Leeds

H EDELSTON

PENICILLIN HYPERSENSITIVITY

SIR,—I was interested in Dr Sims' letter[2] in which he says that he is not aware of any record of anaphylaxis, following the oily injection

Since I started my work in Indonesia in September, 1956, I have seen three serious cases of anaphylaxis following the use of the oily suspension of procaine penicillin, of which one was fatal and the other two very severe I have also seen many less serious reactions

In Indonesia much penicillin in oil is used, because there are lots of remote places where distilled water is hard to get The oily suspension is ready for immediate use and not quickly perishable Many antibiotics are used here without medical control they are available on every market and can be bought by everyone, so that misuse is a common evil

The fatal reaction was in a nurse, whose duties included cleaning the injection syringes She had observed urticaria of the hands, but had not thought of the cause When she asked another nurse to give her a penicillin injection on account of itching, she died within five minutes with œdema of the glottis

One of the other patients was a doctor's wife, who also cleaned the injection syringes regularly After her husband gave her a penicillin injection for bronchitis, she would apparently have died but for an instant injection of adrenaline and anti-histamine

The third severe reaction was in a male nurse's son, who repeatedly received penicillin from his father

Anaphylaxis following the oily injection is a well-known and dangerous complication in this part of the world

Rumah Sakit Umum, Banjumas,
Java, Indonesia

ARIE A HASPELS

SPINAL ANÆSTHESIA

SIR,—I should like to support Mr Lake's pleas (Feb 22) for a renewed interest in spinal analgesia in suitable cases The careful work of Dripps and Vandam[1] and of Thorne[2] is further evidence that large series of spinal analgesics can be given without serious untoward results

But while agreeing that the operating conditions produced by spinal analgesia are good—it anæsthetises as it relaxes as it contracts (the bowel) as it reduces the blood-pressure—all these can be produced by extradural block, with the additional bonus that headaches are unknown (provided the dura is not damaged), and severe central-nervous-system sequelæ are extremely rare May I therefore stress the advantages of extradural block as a method of achieving the beneficial results on the operating-table so ably acclaimed by Mr Lake, using subarachnoid block?

Westcliff-on-Sea, Essex

J ALFRED LEE

POSTMATURITY AND INDUCTION OF LABOUR

SIR,—It is sad to read in *The Lancet* of my colleagues in Britain wasting their time in discussing the dangers of induction of labour in order to avoid the risks to the child of so-called "postmaturity"—risks that have been repeatedly shown to be non-existent Have they not heard of the results at the Chicago Lying-in Hospital where for many years no induction or cæsarean section has been performed for supposed postmaturity?

During the two years 1954–55 there were in that hospital 6593 births The stillbirth-rate was 1 5% and the perinatal mortality 2 7%, both of which included fœtuses and infants weighing 400 g and over The total two-year perinatal mortality in babies over 2500 g was 1% Rooth and Sjöstedt in Lund[3] measured oxygen saturation in umbilical-cord blood in 363 cases, with special reference to the duration of pregnancy There was no apparent change in the oxygen saturation with advancing fœtal age, and no decrease in the mean oxygen saturation in 52 women where pregnancy was prolonged beyond the 42nd week The Belfast workers, Bancroft-Livingston and Neill,[4] came to similar conclusions and found no correlation between the oxygen levels of umbilical venous blood and either fœtal or maternal age

Since the postmaturity addicts apparently believe that the "postmature" fœtus is endangered only in "elderly primigravidæ" (over 26 years) do they think that the placenta in the primigravida differs from that of the multipara? Does the Chicago placenta differ from the British?

Surely a more reasonable explanation of the greater danger of fœtal death during labour in the elderly primigravida is that labour in the elderly primigravida tends to be longer, and that the child in prolonged pregnancy is on the average half a pound heavier If this is accepted, the modern treatment is not induction but trial labour

I beg my young colleagues in Britain (the old ones being mostly beyond hope) to study the new evidence, and to abstain from meddling with women whose pregnancy has, in the course of nature, been prolonged beyond the usual duration Remember, too, the value of the simple check—taking the abdominal girth at its largest level, usually the lower border of the navel—which should (after the 34th week, and making due allowance for excessive abdominal fat or liquor amnii) roughly measure the same in inches as the number of weeks since the first day of the last period Recently I saw a case in point 46 weeks had elapsed since the first day of the last period carefully checked by myself, yet the girth was 38 inches Nothing was done and she delivered herself normally two weeks later But she was a multipara and her placenta was probably different!

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[1] *J ment Sci* 1949 95, 388
[2] *Lancet*, 1957, ii 1067

[1] Dripps, R D, Vandam, L D *J Amer med Ass* 1954 156, 1786
[2] Thorne, T C *Proc R Soc Med* 1954, 47, 301
[3] Rooth G, Sjöstedt, S *Acta obstet gynec scand* 1957, 36, 374
[4] Bancroft Livingston, G Neill D W *J Obstet Gynæc, Brit Emp* 1957, 64 498

Sydney, Australia F J BROWNE

SEPARATION OF MOTHER AND CHILD

SIR,—My attention has been drawn to the fact that various professional workers, both medical and non-medical, are implying that I no longer regard the separation of young children from their mother-figures as a serious mental-health hazard Since this is not so, I should welcome an opportunity to describe my position

My belief is that a misunderstanding has arisen from a paper published eighteen months ago [1] In it we presented the findings of a study in which data derived from teachers' reports and test performances of schoolchildren who had spent long periods in a sanatorium, beginning before their fourth birthdays, were compared with similar data on their classmates Significant differences in the expected directions were found, but it was also true that "more of the sanatorium children than had been expected were reported as able to make friends, and fewer appeared to show the severe disturbances in object relations which underlie persistent delinquency" We concluded that the principal value of the investigation had been "to display the great heterogeneity of personality organisation which is consistent with having undergone a prolonged separation experience starting before the fourth birthday" and, therefore, that "statements implying that children who are brought up in institutions or who suffer other forms of serious privation and deprivation in early life *commonly* develop psychopathic or affectionless characters (e g , Bowlby, 1944) are seen to be mistaken"

Although I believe that in including myself amongst those guilty of overstatement I may have been unduly self-critical, this is not the point of my letter What is of consequence here is that, although the study showed that there was much variation of outcome, it did nothing to cast doubt on the many studies which indicate that *some* children in their personality development suffer grave damage and others lesser damage from a separation experience, nor did it detract in any way from the studies, such as that of Prugh et al ,[2] which confirm the common observation that during a separation experience and after return home a majority of young children are emotionally disturbed Summing up the lessons of our follow-up study we wrote "there are no grounds for complacency The disturbances [found] are serious and affect a far from negligible proportion of children Insofar as measures can be taken to prevent them it remains urgent they be taken"

The position as I see it today is rather like what I suspect it may have been a generation or more ago in regard to poliomyelitis Early workers, impressed by the severity of the aftermath in certain cases of the disease, may well have overestimated the proportion of patients who suffered residual paralysis The fact that we now know that it is only a small minority who are left afflicted has not altered our estimate of it as a serious illness, to be prevented at all costs

There are also differences from the case of poliomyelitis, however In that disease we not only have some idea of the incidence of residual disability but have ready and reliable methods for estimating its degree In the case of personality disturbance following separation and similar experiences we have neither Lacking a basis for calculation, therefore, we are in no position to take calculated risks

Were I now to prepare a revised edition of *Maternal Care and Mental Health*,[3] it would of course be necessary to rewrite part I so as to include many new studies, mostly confirmatory but some not so, and to take account of various criticisms which have appeared Though the picture would appear more complex and the emphasis vary here and there, the overall pattern I believe would look much the same What is more important, the practical recommendations would stand In my judgment the separation of a young child from his mother-figure is not to be undertaken without weighty reasons, and then only provided there is a suitable and stable substitute available to care for him

In conclusion, may I emphasise that the object of this letter is not to persuade sceptics of the correctness of these views but to discourage anyone from supposing that I have changed my position in any material way?

Tavistock Clinic,
London, W 1 JOHN BOWLBY

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—I should like to congratulate Mr Moloney (Feb 8) on the excellent results he has achieved with his nylon-darn repairs of inguinal herniæ To be able to report a recurrence-rate of 0 8% for inguinal herniæ is truly remarkable As far as the surgical public are concerned a critical judgment is based, inevitably, on what they read in the published report Before adopting a nylon darn in my own practice, therefore, I feel that some points in the report need clarification

Mr Moloney disposes of Bassini's operation by saying that the repair lasts only as long as the initial fibrosis due to the catgut, but fifty years ago Bull and Coley,[4] using the Bassini operation, reported 1185 cases with a recurrence-rate of 0 5%, and ten years later, also using a Bassini operation, Hoguet and Coley [5] reported 3725 cases with a recurrence-rate of 0 38% In more recent years O'Connor,[6] using Edmund Andrews' technique, and admittedly with a small series, claimed a recurrence-rate of nil

It is a problem, therefore, to decide which evidence to accept Recently I have pointed out that "recurrence-rates" are almost meaningless,[7] because of the large number of factors which influence the result of all types of herniorrhaphy, and because the number of recurrences in any series is usually unknown, especially as the hernia might recur at any time from the year of the operation to the day on which the patient dies A lifelong follow-up is impracticable, a more limited objective is, therefore, all that can be achieved Mr Moloney's report is based on a follow-up period of five years The length of a follow-up is, however, *less important* than its efficiency

The efficiency of the follow-up is fundamental because there is no known "principle of uniformity" ensuring that the portion of a series which has not been examined will be identical with the portion which has—therefore it is possible that all the patients not followed-up have recurred To increase the length of the follow-up is no answer, if the efficiency declines it makes matters worse For example, if after 2 years, out of a series of 100, 90 cases are found free from a recurrence, the recurrence-rate can be truly stated as 0 0–10 0%, but if after five years only 75 cases are traced, the recurrence-rate becomes 0 0–25 0% in spite of no failures in the 75 cases followed up Again, the position is made worse still if the series is made very large but where the follow-up falls to a half, because if 500 successful cases are traced out of a series of 1000, the recurrence-rate becomes 0 0–50 0% There seems no escape from this uncomfortable conclusion

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1 Bowlby, J Ainsworth, M , Boston, M , Rosenbluth, D *Brit J med Psychol* 1956, 29, 211
2 Prugh D , Staub, E M , Sands, H H , Kirschbaum, R M , Lenihan, E A *Amer J Orthopsychiat* 1953, 23, 70
3 Bowlby, J W H O Monograph no 2 Geneva 1951
4 Bull, W T , Coley, W B *J Amer med Ass* 1907, 49, 1017
5 Hoguet, J P , Coley, W B *Ann Surg* 1918, 68, 255
6 O Connor, J F *Brit med J* 1940, ii 113
7 Doran, F S A *Ann Surg* 1957, 146, 957

Mr Moloney says that 76% of his 219 patients (with 253 inguinal herniæ) were traced. On that percentage, and on the 2 recurrences which were found, the only justifiable statement of the rate of recurrence with nylon darning would be that it lay somewhere between 0.8% and 24.5%.

Lastly, it is not clear from Mr Moloney's paper whether the word "traced" implies that each patient traced was examined at five years. This is important, because it has been my experience, with a routine follow-up clinic, that if the recurrence is small the patient does not notice it. Such a patient would, therefore, give an inaccurate reply to a written questionnaire.

The point that I want to determine, if possible, is the criteria by which the surgical public should prefer Mr Moloney's nylon darn, with a recurrence-rate of 0.8% on 253 herniæ, to Bassini's repair, with which Hoguet and Coley claimed a recurrence-rate of 0.38% in a series of 3725 cases.

Bromsgrove, Worcs — F. S. A. **Doran**

RESPIRATORY INSUFFICIENCY AND THE MORTALITY OF SEVERE HEAD INJURIES

Sir,—The dramatic Copenhagen epidemic of poliomyelitis was responsible for the evolution of the so-called Lassen technique of pulmonary ventilation and toilet, and one wonders what other major catastrophe is required to focus attention on the gravity of the respiratory problem (the term is used in its widest sense) in patients deprived of their protective reflexes from other causes. The article by Mr MacIver and his colleagues (Feb. 22), full of common sense and practical suggestions, reiterates the importance of adequate respiration in a patient suffering from head injury. Just over seven years ago, with head injuries particularly in mind, I listed the factors likely to jeopardise a clear airway, and transport of the patient in the tonsil position, early emptying of the stomach, early tracheotomy, and efficient tracheobronchial toilet were advocated.[1] Despite a further plea by a neurosurgeon[2] it would seem that patients still continue to die unnecessarily ". . . not from their primary injury, but from a chest complication which might have been avoided altogether. . . ."[1]

The Radcliffe Infirmary,
Oxford — R. **Bryce-Smith**

A FUNCTIONAL NECESSITY

Sir,—Dr Beresford (Feb. 22) says that as a result of the present consideration by the Whitley Council of some hundreds of S.H.M.O.s who claim that they are doing consultant work, it seems that a few more consultant posts will be created, and in your comment you pass this presumption without demur.

It appears that both you, Sir, and Dr Beresford are momentarily missing the point of this Whitley investigation. S.H.M.O.s have many grievances, but the one which is at present being considered by the Whitley Council is that in fact these posts already exist, and that what is needed is the payment to the incumbents of the agreed consultant rate for the consultant work they are actually doing, and were appointed to do. The applicants are all men and women who consider that they fulfil certain criteria laid down by the Whitley Committee itself, which are (1) that they hold posts established as consultant posts, or (2) that they hold posts which for the purpose of replacement would be graded as consultant posts, or (3) that they carry out consultant work with full and independent responsibility. Specialty panels composed of eminent members of the specialties concerned have been set up to advise the Whitley Council on how these criteria have been met, and they will shortly present their recommendations, which are to be based on three considerations only—namely, the duties, responsibilities, and quality of the service given.

This has nothing to do with the other aspects of the problems which have resulted from the creation of the S.H.M.O. grade, but is intended as a measure of belated justice to a considerable body of senior hospital staff who since 1948 have suffered a form of exploitation which it would be difficult to parallel.

Shepreth, near Royston,
Herts — C. B. V. **Walker**

INFORMAL ADMISSION OF MENTAL DEFECTIVES

Sir,—In his letter of Feb. 22, Dr Johnson accuses me of a lack of understanding of public sentiment regarding the compulsory detention of mental defectives. I would ask that he and anyone who shares this view refer to my letter in the *British Medical Journal* last May.[1] In that letter I discussed the very points Dr Johnson raises and we are in fact in agreement on most of them. Dr Johnson will realise that I share his disapproval of the detention of an honours B.A. in a mental-defective colony.

I cannot agree, however, with Dr Johnson that the "social incapacity of the so-called feebleminded patient is something entirely different from the defective intelligence of the mentally subnormal", but I suspect from Dr Johnson's subsequent remarks that he is really referring not to the feebleminded but to psychopaths of *normal* intelligence. Feebleminded patients have I.Q.s between about 50 and 70, which, I hope Dr Johnson will agree, represents a true defect of intelligence of the same nature as, but lesser degree than, that of the idiot and imbecile with I.Q.s below 50.

Unfortunately, Dr Johnson does not deal in his letter with my suggestion that an extension of the provisions of section 3 of the Mental Deficiency Acts, to enable the parents or guardian of mental defectives of all grades and ages to place them under hospital care, is a more realistic procedure than the informal method of admission now recommended. From my conversations with my colleagues who appear to favour the informal-admission method, I suspect that they will introduce into their forms of admission and hospital rules conditions which will be indistinguishable from those under section 3, but will be of questionable legal validity and will no doubt be the subject of test cases in the courts.

Does Dr Johnson think a mental defective (I.Q. below 70!) is a fit person to be allowed to leave hospital whenever he wishes without any provision for his future care, for that, I submit, is what informal admission means. I cannot believe that the lay public, whom Dr Johnson represents, would be happy to allow this amount of freedom to their *normal* children under 10 years of age.

Bristol — W. A. **Heaton-Ward**

VOLUNTARY PATIENTS

Sir,—One hopes that the restraints used to prevent voluntary patients from leaving a mental hospital when they wish to do so, as described by Dr Bickford (Feb. 22, p. 423), are not a widely approved practice. Even if such repression does not contravene the letter of the law (inasmuch as a request to leave has not been signed by the patient, who may not have thought of demanding the necessary form), it surely contravenes the principle of voluntary status, and must bring this into disrepute.

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[1] Bryce-Smith, R. *Brit. med. J.*, 1950, ii, 322.
[2] Lewin, W. *Proc. R. Soc. Med.*, 1954, 47, 865.

[1] *Brit. med. J.*, 1957, ii, 1120.

The general public will begin to exclaim "Voluntary? Voluntary, my foot! When you want to leave, they bar your way out, or remove your clothes!"

Of course there is no point in completing legal documents to detain a patient in a compulsory manner when he has volition and does not insist on leaving, and physician-superintendents have, quite rightly, regraded many hundreds of such cases from the certified to the voluntary basis But if a voluntary patient is a danger to himself or others and insists on leaving, he should be detained properly by certification, not improperly by having all his clothes removed

Park Prewett Hospital,
Basingstoke

I ATKIN

Public Health

An Outbreak of Acute Respiratory Infection in West London

WE are indebted to members of the medical staff of the Princess Louise Kensington Hospital for Children for the following account of a recent outbreak of acute respiratory infection in children [1]

Between Jan 20 and Feb 19, 1958, 104 cases of acute respiratory infection were admitted to the Princess Louise Kensington Hospital for Children There was during this time a generally increased incidence of respiratory illness among children in the London area, but to the pædiatricians at this hospital it seemed that not only was the incidence higher in the districts surrounding the hospital than elsewhere, but also that the cases seen there differed in severity and clinical features from cases they were seeing in children's units and hospitals in other parts of London during the same period Of the 104 cases, 86 conformed closely to the pattern outlined below

Clinical picture —In all cases there was a history of a running nose and of sneezing for 3–5 days, sometimes with a cough On the evening before admission the respiration-rate increased and the breathing became noisy, the mother was almost invariably up with her child all night On admission the respiration-rate was found to be raised to between 40 and 96 per min, in many cases there was a rapid rise to between 90 and 140 a few hours after admission The children were pale and shocked, and those under 3 months old were often cyanosed There was tachycardia, especially in the babies under 3 months old, in many of whom the pulse-rate reached 190 There was no peripheral œdema, but in those with extreme tachycardia, the liver was palpable and firm Rib recession was prominent in all cases Breath sounds were harsh, without added sounds at first, though widespread fine râles developed later and persisted for a few days Bronchospasm was uncommon White frothy secretion in the mouth and pharynx, needing frequent aspiration, was noticed in cases admitted more recently Older children were febrile (101–105°F), but the younger and more seriously ill were afebrile Profound anorexia accompanied the onset of the severe symptoms In most cases there was a history of coughs or colds among the family during the week preceding the onset of symptoms

Investigations —Total leucocyte-counts ranged from 6000 to 15,000 per c mm, with no significant disturbance of the ratio of polymorphs to lymphocytes, having regard to the age of the patients In one baby there was a leucocytosis of 30,000 (78% neutrophils) No specific pathogens were isolated from throat swabs, pneumococci were the organisms most frequently found, profuse growths being noted in 18 cases The erythrocyte-sedimentation rate was estimated in 54 cases, this varied from 5 to 45 mm in the first hour, 50% of the results lying between 20 and 35 mm

In most cases, chest radiographs showed generalised increased shadowing, especially in the lower zones, and in a high proportion of these there was frank segmental collapse-consolidation in either upper or lower zones These films were taken after the acute phase of the illness, and in one case only was a radiograph taken in the acute stage This showed massive collapse of the left upper lobe and of the lingula Radiological follow-up examinations show that the lesions are resolving fairly rapidly

Treatment —Oxygen therapy in a tent with a humidifier was needed in 51 cases In 2 of these the oxygen level had to be raised to 95% and the humidity to 100% to overcome cyanosis and respiratory distress, this was achieved by the use of high-tension tents In other cases, an oxygen level of 80% and a humidity between 70 and 80% was found sufficient Duration of oxygen therapy and of digitalisation are shown in the accompanying table (Evidence of cardiac failure occurred only in 6 cases, 5 being under 3 months and another 5 months old) Antibiotics were given in all cases, with sulphonamides in a few, these remedies were chosen at random and all appear to have been without effect other than that of preventing secondary infection 16 babies up to the age of 6 months had to be tube-fed for times varying from 3 to 12 days 2 babies between the ages of 7 months and 1 year had to be tube-fed The importance of a high degree of nursing skill and meticulous attention to detail cannot be too strongly stressed

TREATMENT OF ACUTE RESPIRATORY DISTRESS

Age	0–6 months	7–12 months	1–2 years	2–5 years	Over 5
No of patients	33 (39%)	12 (14%)	11 (13%)	23 (27%)	7 (8%)
No treated with oxygen	22 (67%)	7 (56%)	7 (63%)	12 (56%)	3 (40%)
Duration of oxygen treatment	1–15 days Average 6 days	1–5 days Average 3 days	1/4$^1/_2$ days Average 1$^1/_2$ days	1–6 days Average 2 days	1–3 days Average 2$^1/_2$ days
No digitalised	6				

Progress —A child of 3 months was brought in dead, and another aged 1$^1/_2$ years died half an hour after admission The history of both suggested that they were suffering from this infection Both cases were investigated by the coroner, with results which have not been made known There were no other fatal cases Once the acute stage of respiratory difficulty passed, recovery was rapid

Investigations to determine the nature of this infection are proceeding Dr F O MacCallum has undertaken the virological investigation of nasopharyngeal secretions and of serum, and a survey is being made of family contacts during the days leading up to the onset of symptoms Though their numbers have fallen, cases are still occurring, the peak seems to be passed, but the outbreak is not yet over, and the information in this report may be interesting and useful to others who may yet have to meet this infection in its full severity

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[1] See *Lancet*, Feb 15, 1958, p 371

Mental Hygiene

Preventive psychiatry is, laudably, the mode, so it is fitting that postgraduate students in the department of public health of the London School of Hygiene and Tropical Medicine should be allowed to choose mental health as an elective subject for special study—as they were, for the first time, in the 1956–57 session [1]

Under the tutorship of Dr Morrison Carstairs, of the Institute of Psychiatry, the group met at various institutions Case-demonstrations were used to illustrate the clinical features of disorders and the methods of psychiatric examination The genetic and environmental causes of psychosis were considered, and psychoses were compared with other disorders in the community The group also discussed the legal and administrative provision for commitment to care, treatment (including social therapy), and the attitudes and methods of other countries Neuroses were also considered, including the family doctor's role in prevention and treatment, as well as drug addiction, mental defect, and legal matters A special section of the course was devoted to child psychiatry and discussions about the best way of rearing children The closing stages dealt with the responsibilities in mental health of doctors (who should give sound advice to parents and, about the mentally handicapped, to the whole community) and of the local authorities (in child guidance, care of mentally defective patients, and aftercare of the mentally ill)

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[1] London School of Hygiene and Tropical Medicine Keppel Street, Gower Street, W C 1 Report on the Work of the School for the year 1956–57, p 75

The course proved popular and is being repeated in the present session, and some of the instruction will be included in the main course for the whole D P H class

Pedestrian Deaths in Road Accidents

A survey made by the World Health Organisation[1] in eighteen countries showed that between 1950 and 1955 the death-rate from traffic accidents in pedestrians over 65 increased in all of them except the United States and Ireland, in some countries it more than doubled For younger pedestrians the rates have increased less or even decreased—perhaps because of road-safety instruction of schoolchildren In terms of pedestrians killed annually per million motor vehicles, Japan heads the list with 2336, at the bottom of the list, with 129, is the United States, where there are fewer people walking on the roads (there are 3 inhabitants per motor vehicle there compared with 67 in Japan) The United Kingdom comes in the middle of both lists, with a 16 1% increase in the death-rate of pedestrians over 65, and 390 pedestrians killed per million motor vehicles

Parliament

The Law and the Mental Health Services

IN opening the debate on Feb 19 in the House of Lords on the Royal Commission's report the **EARL OF FEVERSHAM** pointed out that, though it was encouraging that a third of the patients admitted to a mental hospital for the first time were discharged within a year, we must not gloss over the fact that 70–80% of the population of mental hospitals were long-stay patients Furthermore the National Association for Mental Health, of which he is chairman, had reason to believe that every year 80 million man-days were lost to industry through absenteeism due to neurosis These figures, he suggested, showed that mental disorder was widespread and that dependence on mental stability was vital

He welcomed the Royal Commission's recommendations for a revision of the present classification of mentally disordered people and for the discontinuance of certification The new procedures should be regarded by the public simply as a means of providing the patient with the care suitable to his needs Some machinery must exist for the welfare of patients who were unwilling to accept treatment and for the protection of the community The pendulum of public emotion swung dangerously between the desire to lock up every potential murderer in a mental hospital and the belief that all hospitals should be emptied of patients In his view the public needed guidance on these matters

But the most important recommendation in the report was the proposal that responsibility for community care of mental patients should be firmly placed on the local authorities who would provide residential homes and social workers to support patients on their return to their own homes Superintendents of mental hospitals had told him that if this recommendation was put into effect 20,000 long-stay patients could be discharged Lord Feversham added the warning that unless the status of the mental-health services were improved, the patients would be back inside the hospital within a few weeks, and the services could not be improved unless more money was provided Even in these days of financial stringency and the implications of the block grant, the Government must devise some method of giving the local authorities a financial incentive He also suggested that in place of the Board of Control an inspectorate should be set up to ensure that the standards envisaged by the Royal Commission were achieved

He was disturbed that only 2% of the public money spent on the whole of medical research was spent on mental-health research He considered that we needed a permanent foundation investigating the normal behaviour of the human mind If we understood the *normal mind* better, we *should perhaps* see more clearly the causes of mental breakdown Changing the law would not stimulate research, nor would it eradicate mental instability But it could mark the beginning of a resolute campaign to strengthen the mental health and happiness of the nation '

LORD COHEN OF BIRKENHEAD said that in the past twenty-five years increasing recognition of the physical factors which contribute to mental disease had led to a reorientation of outlook on the part of medicine—away from those barracks, even with 2000 or 3000 beds, with monotonously uniformed nurses and monotonously dressed patients, apathetic without any interest or occupation Custodial care for the benefit of society had been replaced by attention to the clinical needs of the individual patient Lord Cohen also stressed the magnitude of the problem 1 in 250 of the population of this country occupied a bed in a mental hospital, 1 child in 20 born in this country would at some time or other have treatment in a mental hospital, 1 child in 10 would suffer from some form of nervous breakdown, and 1 child in 100 was mentally defective A large part of the work of doctors, both in hospital and general practice, was devoted to the treatment of the mentally and nervous afflicted

Within the last few years there had been a remarkable change in public opinion towards the mentally afflicted In 1946 there were about 35,500 admissions to our mental hospitals, but in 1956 there were 88,000 admissions—not because there were more mentally afflicted patients, but because less severe cases were going into the hospitals When he began the study of medicine, only half a dozen general hospitals had a psychiatric outpatient department Today, there were 500 outpatient departments of which 400 were in general hospitals, which showed that there had been an integration of the psychiatric and the physical aspects of illness Experiments were also going on in administration, day hospitals, domiciliary consultation, and so forth He did not think that we could measure the amount of research by the fact that only about 2% of the money spent went to research in mental disease Quite a lot of money was being spent on neurology, anatomy and physiology, which all might have their *bearing on mental health Today we brought to the problems* of the mental patient the whole armamentarium of modern physics, chemistry, and biology

VISCOUNT KILMUIR, the Lord Chancellor, said that the Royal Commission's recommendation that we should abandon the assumption that compulsory procedure must be used unless a patient could express a positive desire for treatment had been widely welcomed The Government had been advised that it could be applied to mental defectives within the terms of the present law, and the Minister of Health had already asked hospitals to regard informal admission as the normal method in future

The Government recognised that until more facilities were available in the community, the hospitals must continue to look after many patients who might eventually be cared for in the community by the local authorities The Government accepted the need for new legislation and that it should be broadly on the lines recommended by the Royal Commission subject to a few modifications considered desirable in the light of views expressed since the publication of the report He could not at the present time give a strict commitment when it would be possible to introduce such legislation

The expansion of the mental health services of the local authorities would not require new legislation For England and Wales the Government fully accepted the principle underlying the Royal Commission's *recommendations* At the same time they must take into account the general and economic financial situation and the *situation created* by the proposed introduction of a general grant instead of a percentage grant for specific services But the Government wished to see development on the lines recommended by the Royal Commission to the fullest extent practicable and intended to invite the local-authority associations to discussions and to make the maximum progress that our resources allow.

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[1] Epidem vit Stat Rep 1958, 11, no 1

University Expansion

ON Feb 20, Mr DERICK HEATHCOAT AMORY, the Chancellor of the Exchequer, made the following statement:

The House was informed in 1956 that proposals had been made by the universities which would increase the number of students from 84,000 in 1955–56 to 106,000 by the mid-1960s, but that the Government believed that the universities should be encouraged to expand even more. Meanwhile, the Government approved proposals for the starting of buildings up to the value of £10·4 million in 1957, £12 million in 1958, and £12 million in 1959.

The existing economic situation imposes on the Government the need for great restraint in this as in other public spending. The Government are satisfied, however, that if the country is to get the increased output of graduates which is needed, and is to secure the full benefits of future advances in science and technology, the current rate of university building programmes must be not only maintained, but increased.

After considering recommendations made by the University Grants Committee, I have given authority for a programme to be prepared on the basis that university building projects will be started up to a value of £15 million in each of the four years 1960–63. This programme must be of a provisional nature and subject to review if the economic situation changes substantially. In saying this, I do not exclude a possible increase in these figures if the economic situation improves and the need can be shown.

It would be difficult to put a precise figure on the increase in the number of university students which will be made possible by a building programme of £60 million over four years. The discussions which took place between the University Grants Committee and the universities were based on an increase to about 124,000 students by the mid-1960s, with the possibility of a further temporary increase of 10% in the second half of the decade, and it should be possible to achieve at least that level with the programme envisaged.

The universities are, in fact, expanding faster than had been expected, and though the future rate of increase cannot be assessed with any confidence the increase beyond 124,000 foreseen for the late 1960s may well prove to be permanent. This will call for great flexibility in planning and will present a challenge to the public spirit and resourcefulness of the universities which I am confident that they will be prepared to meet.

In a written answer Mr Amory added that though their annual reports indicated that most of the universities were dissatisfied in varying degrees with the grants allocated to them, especially for the first two years of the quinquennium, the quinquennial settlement provided for grants which were 8% higher in 1957-58 than in 1956-57, and which rise by a further 30% over the next four years. To these will be added supplementary grants for the cost of the salary awards effective from last August. The result was that the universities were receiving in total 20% more grant in 1957-58 than in 1956-57, and would receive a further 28% increase over the next four years.

Estimates for 1958-59

ON Feb 18 Mr AMORY in introducing the estimates for the coming financial year,[1] announced the increase in the National Health Service contribution to which we referred last week.[2] Discussing the social services more generally, he said that the Government intended to maintain their standards "at the highest level commensurate with a sound economy". But their cost to the Exchequer had steadily increased year by year, and this year's estimates showed further increases in particular for education, the health services, and National Insurance. The rising cost of the health services had caused the Government particular concern, and he reminded the House that when the National Health Service was started the gross cost was expected to be £175 million, of which the Exchequer could bear £126 million. For 1958–59 the estimated gross cost was £740 million. Under the present arrangements the Exchequer's share would be £555 million. This was over four times as much in money terms, and nearly three times as much in real terms, as was originally contemplated. The Government had decided that the whole of this increase could not be borne by the Exchequer. Even on the new rate of contributions the citizen and his employer would be paying in stamps or charges only just under 20% of the gross cost of the service, which was the proportion they were originally intended to carry.

The increased contribution will bring in £24 million in *1958–59* and £32 million in a full year. With its help the estimate for the National Health Service, which would otherwise *have probably gone up by £9–10 million, is actually slightly* lower than for 1958–59. For England and Wales the estimate is £472 million (£485 million in 1957–58) and for Scotland £58 million (£60 million).

QUESTION TIME

Social Insurance Contributions

Mr R H TURTON asked the Minister of Pensions and National Insurance what proportion the proposed weekly contribution for an insured person would bear to the present average weekly earnings in industry, and if he would set out for comparison the relevant proportions at present paid by insured persons in Western Germany, France, and Italy.—Mr JOHN BOYD-CARPENTER replied: The following figures relate only to contributions paid in the social security system of the countries concerned and relate to a differing range of benefits. For instance, in the three Continental countries family allowances are financed out of these contributions.

SOCIAL INSURANCE CONTRIBUTIONS AS PERCENTAGE OF MEN'S EARNINGS

	Employed person's share	Employer's share	*Total*
Great Britain proposed new contribution	*3·9*	*3·3*	*7·2*
France	*6·0*	*30·2*	*36·2*
West Germany	12·2	14·9	27·1
Italy	3·7	46·3	50·0

Poliomyelitis Vaccination

Mr SYDNEY IRVING asked the Minister of Health if he would now authorise the importation from the United States of America of large enough quantities of the Salk vaccine to allow all schoolchildren in the country to be inoculated against poliomyelitis this year, including a third dose.—Mr WALKER-SMITH replied: Vaccination with two injections is at present available for children over six months who were born in or after 1943, expectant mothers, and certain other special groups. I am advised that two injections give a good *degree of protection* and that our first objective should be to increase the *number* of persons so vaccinated. Dr EDITH SUMMERSKILL: Does not the Minister think it would be better to give the third vaccination and thereby ensure that certain people have a guarantee of safety, rather than give two vaccinations only and so allow a lower degree of safety?—Mr WALKER-SMITH: The third injection does not guarantee safety, according to American experience. The Joint Committee on Poliomyelitis Vaccine has recently reiterated its advice that more is to be gained by giving two doses to more persons than by giving *third* doses.

South-West Metropolitan *Regional* Hospital Board

Mr J G MORRISON asked the Minister of Health whether he was now able to announce *his decision on the proposal* to set up a separate regional board for the western area of the South-West *Metropolitan Hospital* Region.—Mr DEREK WALKER-SMITH replied: Consultation of the bodies concerned has shown that the great majority of opinion supports the proposal of the South-West Metropolitan Regional Board for a separate hospital region and board for this area, and I have decided to accept it in principle. But *in* the present financial circumstances I do not consider it justifiable to incur the additional costs *of* administration which would inevitably be involved in the creation of a new board, and I am therefore deferring action until a more appropriate time.

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[1] Vote on Account, 1958–59. H.M. Stationery Office. Pp. 8. *9d.*

[2] *Lancet*, Feb. 15, 1958, p. 419.

Obituary

ALFRED JOSEPH BENATT

M.D. Berlin

Alfred Benatt came to England from Nazi Germany, and his life was one of continuing vicissitude with many disappointments. But at 56 he had the security of many friendships, and his unfailing love of Medicine had made him useful to colleagues, as well as to patients, in distant countries as well as at home.

His chief work was done as a physician and in the prevention of tuberculosis, but his inquiring mind led him first into research, and even before he qualified at Berlin in 1926 he had collaborated in half a dozen papers—mostly on clinical biochemistry. From 1929 to 1933 he was in charge of an institute for cardiology and balneology at Bad Salzuflen in Germany, but he had also worked at Cambridge with Sir Joseph Barcroft on respiratory function tests and on cyanosis—being rescued from an experimental chamber at the last moment, in the manner of the Master. On leaving Germany he spent some time in Lausanne and went to the United States where he drew attention to the plight of German scientific refugees and paid a cardiological visit to Frank N. Wilson's department at Ann Arbor. Eventually a research post was found for him in London at the St. John's Clinic for Rheumatism, but in 1941 the necessities of war took him into clinical medicine, first at the King George V Sanatorium, next at Clare Hall, and then at the Central Middlesex Hospital, where as E.M.S. physician he had charge of the electrocardiographic department and some medical and tuberculosis beds. "When he came to Clare Hall in 1942", writes N. M., "he had already been bombed out three times in London, and before that had experienced the cruel oppression of the Nazi regime—he lost both parents in concentration camps and himself had barely escaped with his life. But his vivacity and zest sustained him so well that we were scarcely aware of the background of suffering, and knew only the active quizzical personality, bubbling with ideas and information—always a stimulus."

Unfortunately the Membership examination was a barrier Benatt never managed to surmount, and without it our medical institutions seemed unable to offer him more than temporary employment as a chest physician or in research. To this medical scholar, happy at a meeting or with a journal, a period of general practice in the Midlands was a difficult experience (he preferred Welsh miners). What was odd was that, even at this time when nobody could give him anything like appropriate employment, he was already treated as a professional equal by people in leading positions. The next few years were to explain why this was so.

At 48 his chance came—though not in altogether congenial form—when the International Refugee Organisation in 1950 put him in charge of two hospitals in the Naples area—one a general hospital with 150 beds and the other a tuberculosis hospital with 130. Strengthened by this experience he went in 1952 to Bangkok as leader of the W.H.O. UNICEF tuberculosis project for Thailand—which he later ably described in these columns.[1] His third venture began in 1954, when he went to Tunisia as medical adviser for the American Joint Distribution Committee—surveying local conditions and training auxiliaries. In each country Benatt found himself a representative and exponent of British ideas and methods in Medicine, and, because of his acquired belief in many of these ideas and methods, he managed to arouse the real interest of colleagues and juniors—Italian, French, and Thai—some of whom have since come to this country through his inspiration.

"This latter period", writes a colleague, "saw the fruition of his earlier endeavours, when he was able to use his knowledge and contacts to lay the foundations for medical advance in communities where it was a paramount need. Not only did he organise the medical and surgical treatment of tuberculosis, he also introduced and rapidly expanded environmental care which previously was non-existent, he visited patients in their homes and huts, worked out methods of segregation and sputum disposal, and taught the elements of prevention and hygiene to his ancillary workers. He saw clearly the importance of overcoming the fundamental difficulties occasioned by the appalling neglect of social and preventive medicine and was stirred to full purpose by what he saw. He was a practical idealist, a man of ability with a positive personality—the type whose work inevitably possesses that quality which makes it survive and grow. Whenever he arrived back from some distant land one sensed that increase in stature which comes from an immense task well and truly done."

"I knew Alfred Benatt for only about eighteen months before he died", writes another associate. "He had returned from working in tuberculosis clinics in some of the less favoured countries. He believed that we, the well-favoured, could do much more to help these countries than we were doing. He tried to continue his own help by writing a simple manual for tuberculosis health visitors and interesting the right people in producing a first-class documentary film on the control of tuberculosis, in order to stimulate and educate a wider audience. In both these projects he was untiring. He had the ability to pass on his own enthusiasm and 'sell' his ideas without rhetoric or obtrusive persistence. His ideas were not new: the attractive novelty was the determination to carry them out. He had no official position or influence, only patent honesty and friends. His small book was almost finished when he died, the film awaited a backer."

In this as in other ways some of his work may be carried on. But "it is as a person that he will be particularly remembered. Many who knew him will think of his kindness as a doctor, his courage in adversity, his delicate humour and courtesy, and the catalytic quality of his conversation—as informative as it was engaging." He died on Feb. 18, and his wife survives him with a son and a daughter.

JOSEPH WILKIE SCOTT

M.C., M.D. Glasg., F.R.C.P.

Dr. Wilkie Scott, consulting physician to the Nottingham General Hospital and Children's Hospital, died on Feb. 16 at the age of 81.

He was born at Airdrie and graduated M.B. from the University of Glasgow in 1898. After holding house-appointments he settled in Nottingham soon after the turn of the century, and he spent the rest of his professional life there. During the 1914–18 war he joined the R.A.M.C. and served with the 1/7th Sherwood Foresters (Robin Hoods) in France. He was awarded the M.C. for his work in organising the defence of an isolated party of survivors in an advanced British trench before Gommecourt and looking after their wounded. Later he was appointed in charge of a medical division in a base hospital.

In his first years in Nottingham he was in general practice, but soon after his return to Nottingham on demobilisation he was appointed to the staff of the General Hospital. He was thus one of the diminishing band of consultants who had begun as general practitioners, and he often said that he had found this experience of great value. He was elected F.R.C.P. in 1933. In 1930 he was president of the Nottingham Medico-Chirurgical Society and in 1938 of the Pædiatric Association. He retired in 1946 to Yoxford in Suffolk and he lived there until he fell ill about two months ago, when he returned to his old hospital as a patient.

W. T. R. writes:

Scott's chief qualities were devotion to work, loyalty, wit, and readiness to help his colleagues and patients. An occasional friendly leg-pull was a characteristic His friendly yet decisive manner was a source of great confidence to his patients and to his colleagues An excellent teacher, he was invariably happy to have with him on his Sunday morning rounds local practitioners, who found them informative and stimulating He was a good committee man, his suggestions practical and helpful A reply to a letter, requiring careful wording and good phrasing, was often left in his hands, and usually met with the agreement of the committee His recreations were golf, tennis, and, in late years, chess, in all of which he met with success and enjoyed the friendship of many of his colleagues After his retirement to Suffolk, he was a regular visitor to Thorpeness and Aldeburgh courses

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[1] *Lancet*, 1956, i, 737.

Dr Scott married in 1926 Dr Marjory Godfrey, she died two years ago and there were no children of the marriage

TOBIAS LEVITT

M A Cape Town, F R C S, F R C S E, F R C S I

Mr Levitt died in Charing Cross Hospital on Feb 22 at the age of 50 after some years of ill health during which he had resolutely continued his research on the thyroid His thesis that most pathological conditions of the gland can be regarded as aspects of a single disease process was set out in his book which was published in 1954

He was a South African by birth and he began his studies in the University of Cape Town, where he graduated M A with first-class honours in anatomy in 1929 and in physiology in 1930 After holding a lectureship in these subjects in the university he came to London and continued his medical studies at the Middlesex Hospital, qualifying in 1934 After holding a demonstratorship in anatomy at the Middlesex Hospital he was appointed a surgeon at Paddington Hospital He took the F R C S I in 1937 During the late war he served in the R A M C as a surgical specialist

After the war most of his time and energy were given to his work on the thyroid He became first assistant at the thyroid clinic at New End Hospital, Hampstead, and in 1952 gave a Hunterian lecture at the Royal College of Surgeons on the status of lymphadenoid goitre, Hashimoto's disease, and Riedel's disease Soon after the publication of his book he was awarded travelling fellowships by the Kellogg Foundation and by the International College of Surgeons He spent the next year lecturing in the United States on diseases of the thyroid Since 1956 he had been attached as a research-worker to the Royal Marsden Hospital while preparing his book on malignant disease of the thyroid gland

For some years he had been a lecturer in surgery to the Fellowship of Postgraduate Medicine, and of his work as a postgraduate teacher W W D writes

Toby Levitt was probably the only person who obtained all three surgical fellowships by examination in the days before the primary was reciprocal Perhaps it was this experience that enabled him to understand so well postgraduates who were striving to pass the final F R C S He will be remembered all over the Commonwealth and particularly in India for the endless trouble he took with these students Many who had abandoned hope of ever passing the examination found new hope with him The various details and hazards of the fellowship were rehearsed continuously what to wear, how to stand, how to speak—no detail was too small for him When the day came, many candidates found the examination an anticlimax, having attended his course in the wards of New End Hospital Generous of heart, he often refused financial reward for his teaching In 1952 his Hunterian lecture held his audience spellbound, and it will long be remembered as a model of its kind His large volume on the thyroid provoked world-wide discussion Produced with the same meticulous care which characterised his teaching, its concepts, although unacceptable to many, were stimulating and thought-provoking, and led to advance in the subject

NORTON MILNER

M R C S

Dr Norton Milner, who died on Feb 12 at the age of 83, was in practice in Sheffield for over fifty years, and for many years he was also anæsthetist to the Sheffield Royal Infirmary

He was born in Sheffield, the eldest son of the late Isaac Milner, J P He studied medicine at the Sheffield Medical School and at University College, London, qualifying in 1898 After spending two years in resident posts at the Royal Hospital, Sheffield, he settled in practice in Millhouses, then a small village near Sheffield To keep up his connection with hospital work he acted as honorary anæsthetist at the Royal Hospital for some years, and during the 1914–18 war, with the rank of captain, R A M C (T), he served as anæsthetist to the 3rd Northern General Hospital in Sheffield and the 59th General Hospital in France After the war he joined the staff of the Royal Infirmary, Sheffield, as an anæsthetist, and was attached to the surgical professorial unit

E F writes

After Dr Milner's elder son joined him as a partner in 1932 he had leisure to cultivate his hobbies of geology and biology He formed a valuable collection of semi-precious stones which he had found and polished, and his advice was sought by jewellers from a wide area He was a keen golfer and for many years was the secretary of a large local golf club During the late war his partner was away for four years, and the extra work of the practice was a great strain to his health During his less active later years he resuscitated his early bibliographical knowledge and interests, and formed a collection of books His life was indeed full but his primary interest was always medicine His ideals of practice were the highest and his numerous patients must be grateful especially for his knowledge of the art as well as the science of medicine

Dr Milner's wife died two years ago He leaves a daughter and two sons

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Appointments

BAIN, G A F, L R C P E, D P M senior assistant psychiatrist, Middlewood Hospital, Sheffield
BUCHAN, A R, M B Durh assistant M O H and school M O, Newcastle upon Tyne
DAY, B L, B M Oxon, F F A R C S consultant anæsthetist, Royal National Orthopædic Hospital, London
DIDSBURY, BRIAN, M B Manc, D P H deputy M O H, school M O, and deputy port M O, Great Yarmouth
GLYNN, CHRISTINA, M R C S school M O, *Birmingham*
GOULD, R A, M B Lond assistant M O, Tadworth Court (annexe of The Hospital for Sick Children, Great Ormond Street, London) Tadworth, Surrey
GRIFFIN, G V, M B Durh assistant M O H and school M O, Newcastle upon Tyne
HAY, A W, M B Durh, D P H area executive M O, south east area and M O H, Whitley Bay, Longbenton *and Seaton Valley*
KAUFMAN LEON, M B Edin, F F A R C S senior registrar in anæsthetics, The Hospital for Sick Children, Great Ormond Street, and University College Hospital, London
MURDOCH, SANDRA, M B Birm, D A anæsthetic registrar, United Norwich Hospitals
PARR D J, M B Lond, D P M part-time S H M O, department of psychiatry, London Hospital.
ROWLANDSON, RICHARD, M B Cantab, F R C S consultant thoracic surgeon, Brook General Hospital, London, and Preston Hall, Aylesford near Maidstone

National Dock Labour Board

JACKSON, J M, F R C S M O, north west region
LLEWELLYN, W A S, M R C S assistant M O, north west region
PHILLIPS, R K, M R C S, D I H M O, south west region

Welsh Regional Hospital Board

HARRIS-JONES, J N, M D Lond, M R C P consultant in general medicine, Llanelly and Bryntirion Hospitals
JENKINS, D C W, M B Lond, D P M assistant psychiatrist (S H M O), Morgannwg Hospital Bridgend, Glamorgan
KOTOWSKI JAROSLAW, M B Edin senior casualty officer, Barry Accident Hospital

Notes and News

CONTROL OF DRUGS IN HOSPITALS

THE Ministry of Health[1] has drawn the attention of hospital authorities to the report by a Subcommittee of the Central Health Services Council[2] on the control of dangerous drugs and poisons in hospitals The Minister broadly accepts the Subcommittee's recommendations, and he asks hospitals to unify their practices, since uniformity has advantages when staff move from one hospital to another

The Minister, though agreeing that the strict checking recommended by the Subcommittee is essential with dangerous drugs and schedule-I poisons, and where calculation or intricate preparation is needed, recognises that strict universal application of the rules is not practicable Where additional cupboards or fluted bottles are needed, these should be obtained as opportunity offers Authorities are asked to take all steps to ensure that every hospital has at least the part-time services of a pharmacist, though shortage of applicants may cause delay

The Minister also refers to the dangers of injecting wrong solutions, and makes recommendations the person giving the drug must always check the label, single-dose ampoules are best, with labelling in the long axis, orders for injectable materials should be not in speech but in clear writing, and full details of premedication (which can be recorded on a label on the patient's wrist) should be studied before any further drug is given

NEW DIRECTIONS IN AUSTRALIA

IN 1956–57, says *Sir Macfarlane Burnet*,[3] there was a significant shift in the orientation of the major work of the Walter and Eliza Hall Institute, of which he is director, the emphasis has been increasingly on immunological topics The auto-immune complement-fixation test was elaborated during attempts to find a complement-fixing antigen, in the livers of people dying of infective hepatitis, specific for infective-hepatitis virus One such liver gave positive reactions with serum from people who had had hepatitis, but similar antigens were found in healthy livers and ultimately in other tissues and other species High titres of reagent were found in the serum in disseminated lupus erythematosus, lupoid hepatitis, and macroglobulinæmia, the reagent is in the γ-globulin fraction (in the macroglobulin fraction in macroglobulinæmia) Dr D C Gajdusek, who developed the test, does not think that there is enough evidence to say whether the reagent is an antibody produced against a modified tissue component or an adventitiously reactive globulin arising for some non-specific reason

CHANGES IN KUALA LUMPUR

Last year[4] we referred to the impressive scope and quality of the research in Malaya at the Institute for Medical Research, Kuala Lumpur The latest annual report of the Institute[5] expresses doubts as to whether this work will continue With Malayan independence is to come replacement of Europeans in the public service by Malayans, and, though expatriates in the Institute may continue to work there until 1965, all might retire with pension and gratuity after last July, and some must retire because of age by 1962 Over three-quarters of the Institute's senior workers are affected, and unhappily local graduates have lately shown little inclination to join the Government medical service Apart from the sad effect on practice of the want of research, a cut in the work of the Institute would deprive clinicians of much of the laboratory assistance that they may now call on We hope that, in the new atmosphere which must come with independence, more local graduates will join the Institute and carry on its indispensable work

EUTHANASIA

THE Euthanasia Society, which bears as its subtitle "a society for obtaining the legalisation of voluntary euthanasia", was founded in 1936 by the late Lord Moynihan In that year a Bill was laid before Parliament to give legal protection to a doctor who acceded to a patient's request for "merciful release" in certain circumstances, particularly intolerable pain associated with incurable disease The Bill was rejected, as was another in 1950, but in the latter case it was thought that the defeat was due to dislike of the complex safeguarding procedure of interviews and documents The society is now concerned to devise a *simpler procedure in the hope that a new* Bill might command more support. It also undertakes propaganda activities, and is anxious to enrol medical members The hon. secretary is Miss G F Fishwick, 86, Rochester Row, London, S W 1

NATIONAL SOCIETY OF NON-SMOKERS

IN its campaign to warn the public against the dangers of smoking and to deter the young from starting the habit, the National Society of Non-smokers has distributed information to public figures, conducted essay competitions for schoolchildren, secured "non-smoking" accommodation in public places, and given advice to smokers who wish to stop the habit but find it hard to do so To support these activities the society needs money, and it asks for gifts to be sent to the honorary secretary, the Rev H V Little, 138, East Dulwich Grove, London, S E 22

NEW SEX GUIDANCE BOOKLET

Into the entirely new version of its booklet *Sex in Marriage*,[1] the Marriage Guidance Council has packed much sound information and advice about the emotional and physical aspects of sex, including contraception. It can be obtained from most bookstalls or by post from the Council, 78, Duke Street, London, W 1

University of Leeds

Mr W P Black has been appointed lecturer in obstetrics and gynæcology

University of Bristol

On Thursday, March 20, at 8 30 P.M, at the Royal Fort, Bristol, Mr T E Cawthorne will give the Patrick Watson Williams lecture His subject will be facial palsy Admission is by ticket obtainable from the registrar, The University, Bristol, 8

University of Edinburgh

The following appointments have been made

Dr Mary Moss, lecturer, general practice teaching unit, Dr Philip Myerscough, lecturer and member of the clinical teaching staff, and Dr Morton Pearson, member of the clinical teaching staff, obstetrical and gynæcological department, Mr John Chalmers, lecturer, orthopædic surgery department, and Dr Ian Smith, assistant, pathology department

Noise

A conference on this subject, dealing particularly with noise in industry, organised by the British Occupational Hygiene Society, will be held in London on Tuesday, April 1, at 11 15 A.M

Mr T E Cawthorne will speak on the physical disturbances produced by excessive noise, Dr T S Littler on techniques of measuring noise, Dr A E Carpenter on the disturbance of mental performance caused by noise, and Mr N Fleming and Mr W C Copeland on the suppression of noise Further details can be had from the hon scientific secretary, Dr D Turner, Associated Ethyl Company Limited, Ellesmere Port, Cheshire

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[1] H M (58) 17

[2] Central Health Services Council Report of the Joint Subcommittee on the Control of Dangerous Drugs and Poisons in Hospitals H M Stationery Office 1958 See *Lancet* Feb 22 1958 p 422

[3] Walter and Eliza Hall Institute of Medical Research Melbourne the director's thirty-eighth annual report 1956–57

[4] *Lancet* 1957, i 1306

[5] Annual Report of the Institute for Medical Research for 1956 Kuala Lumpur 1957 Pp 131 $2 50

[1] The National Marriage Guidance Council Sex in Marriage Pp 24. 1s (postage 3d)

Royal College of Surgeons of England

On Wednesday, March 19, at 4 P M, Prof W D M Paton will give the Joseph Clover lecture of the Faculty of Anæsthetists on mechanisms of transmission in the central nervous system On Friday, March 28, at 4 30 p m, Sir Stewart Duke-Elder will deliver the Lister oration on the emergence of vision in the animal world Both lectures will be given at the college, Lincoln's Inn Fields, London, W C 2

Royal Faculty of Physicians and Surgeons of Glasgow

The Faculty is to receive £20,000 from the Bloch Trust *to meet the cost of a new lecture theatre* (*Manchester Guardian*, Feb 22, 1958) The trust, a charitable foundation of over £400,000, was set up a few years ago by Sir Maurice Bloch

National Association for Maternal and Child Welfare

This association is holding its annual conference from June 24 to 27 in Glasgow The subject will be the changing emphasis in maternal and child care

The speakers will include Sir Kenneth Cowan, Dr Angus Thomson, Dr C D Williams, Dr Andrew Curran, Dr F H Stone, Dr Samuel Harvey, Dr Margaret Scott, Dr W W Fulton, and Dr R A Shanks Further particulars may be had from the secretary of the association, Tavistock House North, Tavistock Square, London, W C 1

Mental Health in the Public-health Field

The northern branch of the National Association for Mental Health, with the department of adult education and extramural studies of the University of Leeds, will hold a residential course on this subject for medical officers of health from April 11 to 19 Further particulars may be had from the branch secretary, 9, Mount Preston, Leeds 2

New Academy in Singapore

Specialists in all branches of clinical medicine in Singapore have lately formed an Academy of Physicians and Surgeons The office-bearers for 1957-58 are

Master, Prof G A Ransome, assistant master, Prof E S Monteiro, scribe, Mr Y Cohen (Surgical Unit A, General Hospital, Singapore, 3), bursar, Dr G H Garlick, bedel, Mr D W C Gawne, censors, Prof R J S Tickle and Dr C E Field

Life Insurance Medical Research Fund of Australia and New Zealand

This year this fund will award grants in aid to institutions and research fellowships to stimulate and support research on cardiovascular function and disease Application forms may be had from Dr J H Halliday, medical director of the fund, 87, Pitt Street, Sydney, N S W The closing date is July 1

Owing to the illness of Sir Geoffrey Jefferson the Hugh Cairns memorial lecture, which was to have been given to the Society of British Neurological Surgeons on March 14, has been postponed

Courses for candidates for the D M R D and D M R T starting in October, 1958, are now being organised by the Faculty of Radiologists Further information will be found in our advertisement columns

On March 26 Wolverhampton Town Council, at a special meeting, will consider the recommendation of their general-purposes committee that the honorary freedom of the borough be conferred on Dr J H Sheldon

The Chartered Society of "Queen Square" will shortly hold an election for vacant pensions (£20 per annum each) These are awarded to needy patients with incurable nervous diseases Forms of application may be had from the secretary of the society, Queen Square House, Queen Square, London, W C 1

The tenth anniversary of the foundation of the "British volume" of the *Journal of Bone & Joint Surgery* was celebrated in London on Feb 14, at its editorial office at 82, Portland Place, W 1 Sir Walter Mercer, as chairman of the British editorial board, presented a salver to the British editor, Sir Reginald Watson-Jones, and Sir Gordon Gordon-Taylor paid an external tribute to this orthopædic enterprise The journal is published in ten annual numbers, of which four are British The American editorial office is at 8, The Fenway, Boston, Mass

Diary of the Week

MARCH 2 TO 8

Monday, 3rd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr Philip Hugh-Jones Mechanical Ventilation in Respiratory Diseases, Bronchoscopy (Films)

Tuesday, 4th

ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Mr C J Dewhurst Problems of Sex and Intersex
INSTITUTE OF NEUROLOGY, Queen Square, W C 1
5 30 P M Prof N F Maclagan Biochemistry of Coma
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Mr A T Gray Cosmetic Materials
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *History of Medicine* Dr A H T Robb-Smith Evolution of Medical Nomenclature
UNIVERSITY OF ST ANDREWS, Queen's College, Dundee
5 P M Mr J F Riley Recipes for Research

Wednesday, 5th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 15 P M *History of Medicine* Dr Ffrangcon Roberts The Medical Contribution to the Rise in Population during the 18th and 19th Centuries
8 P M *Surgery* Dr Marc Iselin (Paris), Mr J N Barron, Mr L W Plewes Hand Injuries
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr Cuthbert Dukes Surgical Pathology of Rectal Cancer
CIBA FOUNDATION
5 P M (26, Portland Place, W 1) Prof Daniel Bovet (Rome) Experimental Basis of Neuroleptic and Tranquillising Therapy
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr J L Livingstone Pros and Cons of Steroid Therapy for Asthma
INSTITUTE OF DERMATOLOGY
5.30 P M Dr R W Riddell Role of Yeasts in Skin Diseases
OXFORD UNIVERSITY
5 P M (*Radcliffe Infirmary*) Dr C W Taylor Value and Limitations of Laboratory Investigations in Gynæcology (Litchfield lecture)
MIDLAND MEDICAL SOCIETY
8 15 P M (Birmingham Medical Institute, Edgbaston) Dr Philip Gell The Paradox of Allergy
NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY, 64, St James's Street, Nottingham
8 30 P M Prof John Bruce A Surgical Gossip
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School) *Medicine* Prof Melville Arnott Regional Blood Flow in Health and Disease
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (18, Nicolson Street) Mr R C Lowe, Dr J A Simpson Cerebro-vascular Accidents

Thursday, 6th

ROYAL SOCIETY OF MEDICINE
5 P M *United Services* Major R J C Hart, Surgeon-Major G H Bulow, Lieut-Colonel R M Johnstone, Colonel T M Pace Respiratory Tract Infection
8 P M *Neurology* Dr D H M Woollam, Dr J W Millen, Dr William Blackwood, Mr Joe Pennybacker Vascular Disease of the Spinal Cord
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8 30 P.M Prof J Trueta Medicine in Brazil
MIDLAND THORACIC SOCIETY
7 30 P M (Queen Elizabeth Hospital, Edgbaston) Dr E G L Bywaters Collagen Diseases as they Affect the Lungs
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
4 30 P M (with Manchester Medical Society) Dr Ralston Paterson Breast Cancer—Preliminary Report of Two Clinical Experiments Mr Ian Orr Surgical Surprises in the Small Intestine

Friday, 7th

ROYAL SOCIETY OF MEDICINE
5 30 P M *Anæsthetics* Dr H C Churchill Davidson, Dr C F Scurr, Dr A J Beard *The Extracorporeal* Circulation
POSTGRADUATE MEDICAL SCHOOL
10 A M Mr H S Shucksmith Surgery of Arteriosclerotic Arteries
4 P M Prof R E Tunbridge The So-called Collagen Diseases
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Mr Charles Heanley *Facial Reconstruction*
YEARSLEY LECTURE
5 15 P M (1, Wimpole Street, W 1) Mr Francis McGuckin Recent Developments in Tympanoplastic Surgery

Births, Marriages, and Deaths

BIRTHS

MANN.—On Feb 20, to Joy, wife of Dr Trevor P Mann—a sister for Michael, Nicholas, and Philip

DEATHS

CONLIN.—On Feb 4, in Middlesbrough, Arthur Conlin, M B Dubl

A semi-permanent exhibition on cytology, by Dr Henry Haber, will be held from March 7 to 28 at the Institute of Dermatology, Lisle Street, London, W C 2

The Lancet · Saturday 8 March 1958

ENVIRONMENTAL PENICILLIN AND PENICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

J C GOULD
B Sc, M B Edin
LECTURER IN BACTERIOLOGY IN THE UNIVERSITY OF EDINBURGH

WORLD-WIDE reports agree that penicillin-resistant strains of *Staphylococcus aureus* recovered from patients in hospital have increased from a small proportion of the strains tested shortly after the introduction of penicillin (Rammelkamp and Maxon 1942, North and Christie 1945, Blair et al 1946, Beigelman and Rantz 1950) to 50–90% at the present time (Barber 1947a and b, Barber and Rozwadowska-Dowzenko 1948, Barber and Whitehead 1949, Dowling et al 1953, Finland and Haight 1953, Gould and Allan 1954) These strains are most prevalent among hospital inpatients, and smaller numbers have been isolated from hospital outpatients (Voureka and Hughes 1949, Rountree et al 1951, Summers 1952) and the general population in the same geographical areas (Forbes 1949, Martin and Whitehead 1949, Vogelsang 1951, Linsell 1952, Dowling et al 1953, Gould and McKillop 1954, Roodyn 1954, Rountree et al 1954), whereas they are rare in communities where penicillin has not been administered (Hopps et al 1954, Rountree 1956)

All naturally occurring penicillin-resistant staphylococci produce penicillinase, by virtue of which they are resistant to penicillin (Spink and Ferris 1947, Barber and Rozwadowska-Dowzenko 1948, Finland and Haight 1953, Florey et al 1949) A few strains of apparently penicillin-sensitive *Staph aureus* have been shown to contain penicillinase-producing variants, and these variants probably arise by mutation (Demerec 1945, 1948, Szybalski 1953) and possibly also by adaptation (Hinshelwood 1952, Barber 1953), but in either case their growth and further spread will be favoured by selective factors in the environment, such as penicillin

The first described strains of penicillin-resistant *Staph aureus* were observed in patients under treatment with penicillin (Rammelkamp and Maxon 1942, Blair et al 1946, Harley et al 1946), and it was considered that the resistant mutants were selected by the penicillin The subsequent increase of penicillin-resistant strains in hospital inpatients and other persons treated with penicillin (Gould and McKillop 1954) may thus be explained on the basis of their frequent treatment with penicillin

However, the proportion of penicillin-resistant strains of *Staph aureus* is increasing among carriers in hospital who are not receiving penicillin This is usually explained by postulating a free interchange of organisms between the treated patients and these carriers (Knight and White 1956), but this presupposes that the penicillin-resistant organism has the power to replace the naturally occurring penicillin-sensitive carrier strains So far there is no satisfactory evidence that this happens

Further, if mutation takes place in each patient under treatment, a much greater variety of phage-types of penicillin-resistant staphylococci would be expected to occur in hospitals, whereas it is usual for only a few strains to be present in each hospital (Gould and Allan 1954, Maccabe and Gould 1956)

Also, patients infected with penicillin-sensitive strains before treatment would be expected to yield penicillin-resistant strains of the same type following treatment. In fact, most cases that are investigated show the penicillin-resistant strains to be of different type from the sensitive strain originally present

Another possible explanation of the rapid colonisation of carriers in hospital is that these persons receive in their noses enough penicillin inhaled with air and dust and transferred from their hands and fingers to maintain a nasal concentration of penicillin inhibitory to sensitive staphylococci This would be important because the anterior nares are the primary site of colonisation in the carrier, and the staphylococci are disseminated from the nose to other parts of the body of the carrier and to his clothes, to the air and dust, to fomites, and to other persons

Evidence for this hypothesis was sought by testing the environment in a hospital for free penicillin and comparing the results with those found in a factory handling penicillin where penicillin-resistant staphylococci had been found to predominate among carriers (Gould 1957)

Materials and Methods

The hospital examined was a large general hospital with about 900 doctors and nurses Permanent nasal carriers comprised 53% of the staff, and the proportion of these carriers harbouring penicillin-resistant strains exceeded 90%

The factory examined handled penicillin from bulk and dispensed it in various forms—crystalline, procaine, oily, and incorporated in creams Other antibacterial agents were also handled

Recovery of Penicillin

Penicillin was recovered on indicator plates, which were petri dishes cast with agar uniformly sown with a penicillin-sensitive microorganism, usually a staphylococcus susceptible to 0 02 μg of penicillin per ml After incubation, zones of inhibition of growth indicated antibacterial activity That the zones of inhibition were due to penicillin was proved by inoculating a penicillin-sensitive staphylococcus on to one part of each zone of inhibition, and this staphylococcus plus penicillinase on to an adjacent part If inhibition was due to penicillin, the staphylococcus grew on the penicillinase-treated area only This proved that the inhibition was due to penicillin

The penicillin content of the air was measured by directly exposing indicator plates to settling particles (settling plates) and also by means of an impinger sampler, taking 25 c ft of air a minute through 400 small holes on to an indicator plate (the instrument was a modified Du Buy and Crisp sieve-plate-sampler with a collection efficiency of about 60% for particles within the range 1-5 μ, and probably nearly 100% for particles of 20–100 μ) Most of the areas of inhibition of growth on the indicator plates were circular and discrete and must have resulted from a single particle of penicillin The concentration of penicillin required to produce equivalent zones of inhibition was obtained by comparison and calculation

Indicator plates identical with those used in the sampling experiments were prepared Various concentrations of penicillin were placed in these plates, either in the form of saturated paper discs or as tiny drops of penicillin solution The diameters of the zones of inhibition of growth were measured and plotted on a graph against the amounts of penicillin in the series

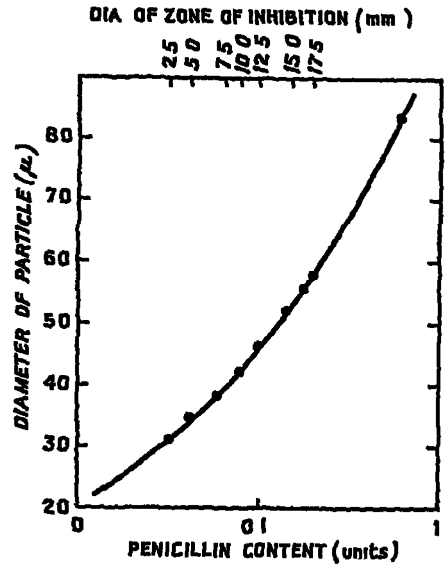

Fig 1—Relation of diameter of zone of inhibition on *indicator plate* to penicillin content and size of particle The scale of penicillin content is logarithmic

On the basis that the particles recovered from the air consisted either of pure procaine penicillin or of the sodium salt of benzyl penicillin, an equivalent particle-size was calculated and a graph prepared relating the zone of inhibition of growth to penicillin content and size (fig 1) The smallest amount of penicillin giving a definite zone of inhibition of growth in these experiments was 0 02 μg This amount of procaine penicillin was contained in a sphere 36 μ in diameter, and of sodium benzyl penicillin in a sphere 32 μ in diameter Indefinite zones of inhibition were due to smaller particles, and particles of pure penicillin less than 25 μ did not give individual zones of inhibition and could only be detected when enough of them aggregated at one place on the medium to produce recognisable inhibition

Sampling of Penicillin from Other Sources

The presence of penicillin on fomites was demonstrated in an approximate manner by swabbing the surface of the fomite with dry or wet swabs and rubbing these swabs thoroughly over the surface of an indicator plate Inhibition of growth indicated the presence of penicillin Fingers and hands were tested for contamination with penicillin by impressing the finger on an indicator plate

The anterior nares were sampled most successfully by smearing the skin lining the nasal vestibule with a water-lanoline cream and, after a suitable interval, removing some of the cream with sterile filter-paper discs and transferring the discs to indicator plates

TABLE I—ENVIRONMENTAL PENICILLIN IN HOSPITAL

Hospital site	Amount of penicillin settling on 12 sq in per hour (μg)	Penicillin content of air per 100 c ft measured by sieve sampler (μg)	Presence of penicillin on fomites	Presence of penicillin on hands and in nares of staff
Inpatient department				
Doctors rooms	0–0 02	Not tested	Not tested	Not tested
Corridor	0–0 05	Not tested	Not tested	Not tested
Medical ward	0·06–0 10	Trace–0 4	Not tested	Not tested
Surgical ward	0 05–0 25	Trace–0 5	Not tested	Not tested
Dispensary	1 0–1 70	0 5–35 0	Not tested	Not tested
Outpatient department				
Minor surgery room	1·0–5·0	1–50	Present	Present
Dressing-rooms	0 5–1·0	1–15	Present	Present
Corridor	0–0 15	Trace–0 6	Not tested	Not tested
Waiting-room	0–0 20	Trace–1 0	Not tested	Not tested
Small ward	0–0 05	Traces	Present	Present
Doctors room	0–0 05	Not tested	Not tested	Not tested
Operating-theatre	0	0	Not tested	Not detected

Detection of Nasal Carriers of Staph aureus

Nasal carriers were detected by swabbing the anterior nares and culturing the swabs on milk-agar (Mackie and McCartney 1953) Staphylococcal colonies were tested for the production of coagulase (Fisk 1940, Cadness-Graves et al 1943), penicillin sensitivity (Gould and Bowie 1952), and the production of penicillinase (Gots 1945), coagulase-positive strains were further tested for susceptibility to a standard set of bacteriophages

Results

AIR SAMPLING IN HOSPITAL

The results of sampling air in various parts of the hospital show that penicillin was *present in variable* amounts in the air or in the dust of all the sites tested Table I shows the amount of penicillin detected by the settling plates and the amount recovered by sampling the air with the sieve sampler The smallest amounts of penicillin were found in the doctors' side-rooms, where penicillin was presumably never handled Larger amounts were found in open medical and surgical wards, as well as in some corridors The dispensary air contained a great deal of antibiotic activity, especially nearest the room where antibiotics were dispensed A proportion of the activity was due to penicillin The highest levels, however, were recorded in parts of the outpatient department, and this site was examined in greater detail and was especially suitable because penicillin was the only antibiotic used at that time

Results of Sampling Outpatient Department

Within the department the amount of penicillin recovered varied greatly but was highest where penicillin was being administered—in the rooms used for minor surgery During this investigation very little penicillin was being used or given to patients in any other part of the department The amounts of penicillin recovered fell off rapidly with the distance from the incision rooms, and very small amounts were recovered from the doctors' retiring-room and the operating-theatre, which were geographically farthest removed (table I)

Examination of Persons and Fomites in Outpatient Department for Penicillin

Fomites were handled and the hands, previously shown to be free from antibiotic activity, were impressed on indicator plates Amounts of penicillin sufficient to inhibit growth over the full plate were obtained in many instances after a few seconds' handling of articles such as trays, caskets, instrument-tray covers, dressing containers, and bottles in the dressing-rooms and rooms used for minor surgery (table I) The doctors' and nurses' hands were examined before washing at various times during the day Amounts of penicillin sufficient to inhibit large areas of indicator plates were present on the hands and fingers of about half the doctors and nurses Apparently these persons had picked up the penicillin from fomites by handling in the natural course of their duties No attempt was made to estimate quantitatively the amounts present on the hands or the fomites

Examination of Anterior Nares for Penicillin

The anterior nares of some of the doctors and nurses were tested This was a crucial matter because if environ-

TABLE II—NASAL CARRIAGE OF *Staph. Aureus* AMONG MEMBERS OF STAFF OF HOSPITAL OUTPATIENT DEPARTMENT AND DETAILS OF CARRIER STRAINS

Individuals	Presence of *Staph. aureus* in nares	Penicillin susceptibility of nasal strain	Bacteriophage types	Penicillin in nose and/or hands
Surgeon 1	+++	Resistant	6/7/47/54	0
Surgeon 2	—			0
Surgeon 3	++	Resistant	52/52A/80	0
Surgeon 4	—			0
Surgeon 5	+++	Resistant	52/52A/79/80	Present
Surgeon 6	—			Present
Nurse 1	+++	Resistant	7/54/73/77	0
Nurse 2	++	Resistant	7/54/73/77	Present
Nurse 3	—			Present
Nurse 4	+++	Resistant	52/52A/80	Present
Nurse 5	+++	Resistant	52/52A/79	Present
Nurse 6	+++	Resistant	NT	0
Nurse 7	—		—	0

0 = none detected

mental penicillin affects the growth of *Staph. aureus* it is most likely to do so in the nostrils, the primary site of colonisation in the carrier, and a selective concentration must be present at least for a considerable time. The results showed that all members of the staff working in the incision and dressing rooms, and four out of eight working in other parts of the department, had easily detectable penicillin in their nares after a morning's work. Whether this penicillin had been inhaled from the air or introduced by contaminated fingers cannot yet be told.

Nasal Carrier-rate of Staph. aureus *among Staff of Outpatient Department*

The carrier-rate exceeded 60%, and all the doctors and nurses who were carriers harboured penicillin-resistant strains (table II). The number of colonies of *Staph. aureus* isolated from carriers from whom detectable penicillin was recovered from the nares was significantly less than in those carriers who had no detectable penicillin in their nares.

EXPERIMENTAL CONTAMINATION OF A ROOM WITH PENICILLIN

Experiments were made in laboratory rooms to show that the air and dust can be contaminated when penicillin preparations are used and handled, as they were in the outpatient department of this hospital. A hard surface was contaminated by spilling, dropping, and squirting penicillin solution (sodium benzyl penicillin) and suspensions (procaine penicillin) in concentrations calculated to simulate those that would be used during the preparation and giving of penicillin injections and the washing out of the penicillin-contaminated syringes.

TABLE III—RECOVERY OF PENICILLIN IN A ROOM CONTAMINATED BY 100,000 UNITS OF PROCAINE PENICILLIN

—	Time after contamination or reagitation (min.)*	Penicillin settling on indicator plates of 12 sq. in. area per hour at 5 metres distance from source of contamination (μg.)	Penicillin content of 100 c. ft. of air by sieve sampling (μg.)
Before contamination	—	0	0
After initial contamination	1–5	2·0–5·0	10·00
	6–10	0·32	4·00
	11–15	0·11	2·00
	16–20	0	1·50
	21–25	0·02	0·05
	26–30	0	0
After reagitation	1–5	5·0	5·00
	6–10	0·6	3·20
	11–15	0·1	1·10
	16–20	0·2	Trace
	21–25	Trace	0
	26–30	0	0
	30–40	Trace	0

* Smooth surface of a piece of hardboard 4 ft. by 3 ft. contaminated with penicillin. Reagitation after drying by striking ten times on the under-surface.

The preparation of an injection of penicillin usually involves adding a few millilitres of water to a phial of dry penicillin, and a solution or a suspension containing 300,000–600,000 units of penicillin per ml. is sucked up into a syringe. Our observations indicate that about 0·2 ml. remains in the syringe and needle after the injection, equivalent to 60,000–120,000 units, and this amount is diluted to various degrees by cleaning the syringe.

Measurements were made before and after the contamination procedures by exposing indicator plates and sieve sampling. After the contaminated surfaces had dried, dust was raised by agitation, and measurements were continued. The results (table III) showed that a previously penicillin-free room was contaminated, and exposed indicator plates and sampler plates showed zones of inhibition of growth comparable with those obtained in the hospital environment. The frequency of occurrence of particles of different calculated sizes corresponded to those found in hospital, and a greater proportion of large particles were detected on the settling plates than on the sampler plates (fig. 2).

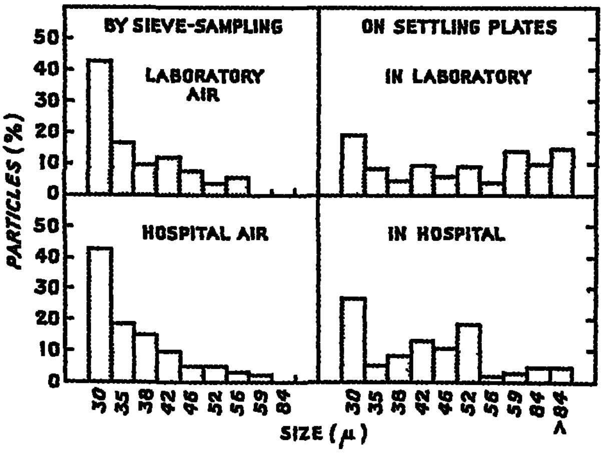

Fig. 2—Distribution of sizes of penicillin particles.

Direct observation of the particles of penicillin in suspensions and crystals formed during evaporation of solutions showed that the size distribution corresponded to the distribution observed in hospital and in the contaminated laboratory room for particles of 30 μ or more. There were many particles smaller than 30 μ, but these are too small to be detected individually on the indicator plates. This seems to confirm that it was the particles and crystals from the penicillin preparations which contributed most to the contamination of the hospital environment (fig. 2).

If the air in the contaminated room remained still and there was no further activity, the amount of penicillin recovered on settling plates and by sieve-sampling rapidly became less with time until after 25 minutes it was exceptional to recover any penicillin. Disturbance of the air and dust produced recirculation of penicillin-contaminated particles, and these could be recovered for a further 20–25 minutes, depending on the degree and continuance of agitation. This is to be expected from the relatively large size of the penicillin particles involved, because those larger than 25 μ will settle to the ground and other surfaces in a matter of a few seconds (Duguid 1946).

TABLE IV—NASAL CARRIAGE OF *Staph aureus* AMONG STAFF OF FACTORY AND CONTROLS OUTSIDE FACTORY, CHARACTERISTICS OF THE CARRIER STRAINS, AND AMOUNT OF PENICILLIN RECOVERED FROM FACTORY ENVIRONMENT

Group	No of persons	Carriers of *Staph aureus* (%)	Average no of staphylococci on nose swabs	Carrier strains (%)				Penicillin recovered from 100 c ft samples of air	Penicillin on fomites	Penicillin in nares or on hands of staff
				Penicillin-resistant	Phage group					
					I	II	III			
Penicillin filling-rooms and packing-rooms	44	9	+	100	25	0	75	Filling-room 10–250 μg Packing-room 2–30 μg	Large amounts	Present in those examined
General packing-room (no penicillin handled)	32	27	+++	100	36	0	60	Small amounts of penicillin (variable amounts of other antibacterial agents)	Not tested	Not tested
Office	28	32	+++	100	30	0	70	Traces of penicillin	Not tested	Not tested
General population outside factory	36	30	+++	12	27	64	9	Not tested	Not tested	Not tested

EXAMINATION OF FACTORY AND FACTORY PERSONNEL

The staff of this factory were first examined for nasal carriage of *Staph aureus* and for this were divided into three groups (1) those working in contact with penicillin, (2) those working in the factory but not with penicillin, and (3) administrative staff working in a separate building and not coming into continuous contact with the factory itself At the same time a fourth group, of persons from a general practice in the same geographical locality, were similarly examined, being chosen because they had no contact whatsoever with the factory or its personnel

The carrier-rates for these groups and the penicillin sensitivity and bacteriophage type of the carrier strains of *Staph aureus* are shown in table IV The nasal-carrier strains isolated from factory personnel resemble those commonly found in hospitals both in their resistance to penicillin (due to the production of penicillinase) and in the limited number of types present Most of the strains were of group-III types and quite distinct from those isolated from carriers among the general population group, who had a nasal carrier-rate similar to that found in any non-hospital community The proportion of penicillin-resistant strains was also normal It is significant that no penicillin-sensitive staphylococci were isolated from any of the factory staff or from the environment examined It is also noteworthy that only small numbers of microorganisms were isolated from the nares of persons working in close contact with penicillin, and this is correlated with a very low carriage-rate of *Staph aureus* among such persons Penicillin was detected on the fingers and in the nares of those working in the penicillin filling and packing rooms

The next experiment was to measure the penicillin content of the air at various sites in the factory The results are shown in table IV Appreciable amounts of penicillin were recovered from the air in several parts of the main factory building, where penicillin was dispensed or handled, and much smaller amounts where other drugs were handled Only traces of antibacterial activity were detected in the air of the administrative building

The concentration of penicillin in the air of the penicillin filling-room and packing-room appeared to be sufficient to depress a growth of all bacteria in the nares of persons working there, and the strains of staphylococci isolated all produced penicillinase Small amounts of penicillin were recovered from the air of other parts of the factory, which, though insufficient to depress the growth of nasal flora, was adequate to select and maintain penicillin-resistant strains of *Staph aureus* Although little penicillin could be detected in the air of the administrative block, probably traces of penicillin would reach this site by air and in dust and on the clothing and fingers of members of staff Thus penicillin could be transferred to their nares and be effective in maintaining strains of penicillin-resistant staphylococci

Discussion

It is clear from these observations that penicillin was found in highest concentration in the environment where it was being used In the dispensaries, hospital wards, and outpatient departments of this hospital the handling of penicillin-containing phials and syringes seems to be the more important source Leakage from the phial during puncturing, clearing of air bubbles and froth from syringe and needles, and spraying when washing out the syringe commonly takes place during the process of injecting a patient Other sources are as obvious, such as insufflation of the wounds with penicillin and the use of other topical preparations of the penicillin Some are not so obvious, such as the spilling of urine containing penicillin from a treated patient Air may therefore be contaminated in two ways directly, by droplet nuclei, which are the dried residue of droplets atomised from syringes and the like, and indirectly, by the raising of dried spilt penicillin as dust

The hospital environment can therefore readily acquire penicillin, and the amount may be cumulative because destruction of the dried penicillin in dust may be relatively slow, and the penicillin would continually be redistributed through disturbances of dust and air and the handling of articles Appreciable amounts of penicillin have been shown to gain access to the nares of persons working in the hospital environment, and without doubt this will inhibit the growth of penicillin-sensitive strains of *Staph aureus* Such persons will be continually exposed to recontamination with staphylococci from the environment, the great majority of which in hospital will be penicillinase-producing strains Penicillin-resistant strains will therefore find it easy to establish themselves (Clarke 1957) and t colonise the nares of a larger number of persons i hospital than in other environments which do not contai penicillin and where the nares of most carriers ar colonised with penicillin-sensitive *Staph aureus*

Thus the predominance of penicillin-resistant *Staph aureus* in carriers in a closed community such as a hospita is explained, as also is the fact that the longer the perio of exposure to the hospital environment the greater i the chance of becoming colonised with penicillin-resistan organisms (Barber et al 1949, Cairns and Summer 1950, Rountree and Barbour 1951, Vogelsang and Bo 1952, Lepper et al 1953, Hutchison et al 1957 Carriers among the general population are not affected because they would have little chance of accumulation o penicillin in their homes and little chance of cross-infection with resistant strains of staphylococci

If environmental penicillin is important in maintaining penicillin-resistant staphylococci in this way, one would expect that any community exposed to environmental penicillin, as distinct from therapeutic administered penicillin, would have a higher incidence of penicillin-resistant strains That this is so is clearly shown in the results obtained in the examination of the penicillin factory, where persons exposed to environmental penicillin but not to administered penicillin had as high a resistance-rate of *Staph aureus* as had hospital personnel Therefore, it can be concluded that environmental penicillin is an important factor in the widespread colonisation of hospital carriers with penicillin-resistant strains of *Staph aureus*

Restriction in the use of penicillin and avoidance of contamination of the environment might therefore be expected to reduce colonisation of carriers with penicillin-resistant strains and therefore to reduce spread to patients, with a consequent decrease in the number of infections with penicillin-resistant organisms

Staphylococci resistant to other antibiotics also occur in hospital in proportion to the amount of these drugs used (Clarke et al 1952), and possibly contamination of the environment with these antibiotics is related to the prevalence of resistant strains in the same way as with penicillin In support of this is the evidence that restricted use of chloramphenicol (Kirby et al 1953), streptomycin (Needham and Nichols 1953), and erythromycin (Lepper et al 1953) in hospital is associated with a reduction in the number of strains of *Staph aureus* resistant to these antibiotics

Summary

Penicillin was detected in the environment in a general hospital The amount recovered in different parts of the hospital varied considerably but was greatest nearest those rooms where penicillin was being handled or therapeutically administered

Particles of the penicillin directly contaminate air, dust, and fomites The noses of carriers of *Staph aureus* are contaminated by inhalation and transference from hands and fingers, and this provides a concentration of penicillin adequate to inhibit penicillin-sensitive *Staph aureus* and leaves the nares free for colonisation with penicillin-resistant strains which abound in the hospital environment.

The environment of a factory handling penicillin was similar to that of the hospital in that it contained penicillin and all the carrier strains of *Staph aureus* were penicillin-resistant

It was concluded that environmental penicillin is an important factor in the colonisation of hospital nasal carriers with penicillin-resistant *Staph aureus* and in the cross-infection of persons receiving or not receiving therapeutic antibiotic.

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RECEPTORS IN THE HIGH-PRESSURE AND LOW-PRESSURE VASCULAR SYSTEMS

THEIR ROLE IN THE REFLEX CONTROL OF THE HUMAN CIRCULATION

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THE importance of the carotid-sinus and aortic-arch baroreceptors in the reflex regulation of the circulation has been recognised since the classical experiments of Heymans (Heymans et al 1933) Besides these receptors in the high-pressure vascular system many receptors have been described in the walls of low-pressure vascular components, especially the right and left atria and the intrapericardial portions of the superior and inferior venæ cavæ (Nonidez 1941, Paintal 1953) Neil and Zotterman (1950) and Paintal (1953) described afferent vagal impulses which appeared to be related to the atrial pressure cycle, but the effect of these impulses on cardiovascular activity remains obscure Evidence has been presented that activity of this type of receptor may affect heart-rate (Bainbridge 1915, Coleridge and Linden 1955), vasomotor tone (Brigden and Sharpey-Schafer 1950, Roddie et al 1957a), and output of urine (Henry et al 1956a, Love et al 1957)

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We review here the results of recent experiments designed to elucidate in man the interrelationships between the high-pressure and the low-pressure receptors, with special reference to the control of vasomotor tone in the limbs.

Methods

The experiments were carried out on young healthy male adults. Blood-flow in the hand, forearm, or calf was measured by venous-occlusion plethysmography. Intravascular and intrathoracic pressures (Dornhorst and Leathart 1952) were measured by capacitance manometry. In some experiments deep and superficial forearm veins were catheterised (Roddie et al 1956), and the oxygen saturation of blood sampled from these veins was estimated by a spectrophotometric technique (Roddie et al 1957b). In certain circumstances changes in the oxygen saturation of blood from these veins can indicate changes in muscle and skin blood-flow respectively. In other experiments the nerves to the forearm and hand were blocked by infiltrating the tissues round the ulnar median and radial nerves at the elbow with 2–3 ml of lignocaine with adrenaline 1 : 50,000 (Roddie et al 1957c).

Results

Role of Receptors in High-pressure System

The activity of the stretch receptors in the carotid-sinus area can be conveniently changed by compression of the common carotid arteries below the carotid sinus (Roddie and Shepherd 1957) and by applying suction to the neck area (Ernsting and Parry 1957). These procedures respectively decrease and increase the pressure across the artery walls in the carotid-sinus region. Fig 1a shows some of the effects of compressing the common carotid arteries: the mean pressure at the carotid sinus is about halved, and the pulse-pressure transients are almost abolished; this is accompanied by an increase in systolic, diastolic, and mean pressure in the brachial artery, an increase in heart-rate, and stimulation of respiration. These are the classical changes and are consistent with decreased activity of the carotid-artery stretch receptors.

There is no evidence, however, that the pressor response to carotid compression is even in part due to a reduction in the calibre of the limb blood-vessels. The blood-flow through the hand and forearm is slightly increased, and this small increase can be explained by the increase in the perfusion pressure. Resistance to blood-flow in the limbs, calculated by dividing mean perfusion pressure (mean arterial minus mean venous pressure) by mean blood-flow is either unchanged or slightly decreased. Similarly Ernsting and Parry (1957) have shown that, during the hypotensive response to an increase in effective blood-pressure at the carotid sinus, there is no evidence for an increase in the calibre of the limb blood-vessels.

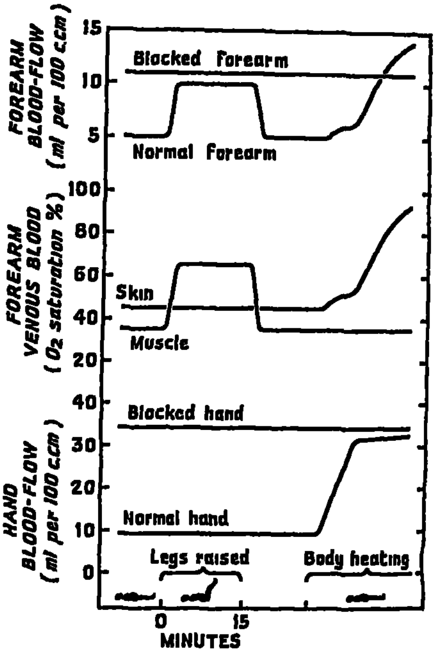

Fig 2—Comparison of effects of passive raising of legs of recumbent person and of body heating on blood-flow through normal and nerve-blocked hands and forearms, and oxygen saturation of blood from superficial forearm vein (draining mainly skin) and deep forearm vein draining mainly muscle)

It therefore seems clear that changes in blood-pressure produced by stimulation of the carotid sinus are not due to changes in vascular resistance in the limbs and must be due either to changes in cardiac output or to changes in resistance in other vascular beds, or to both. Since both muscle and skin in the limbs are richly supplied with sympathetic fibres (Lewis and Pickering 1931, Barcroft et al 1943, Roddie et al 1957c), the failure of the limb vessels to participate in the reflex changes that follow stimulation of the carotid sinus is not a consequence of poor vasomotor innervation.

Role of Receptors in Low-pressure System

Large changes in forearm vascular resistance take place when body posture is changed (Brigden et al 1950, Roddie and Shepherd 1956).

An example of this type of response is shown in fig 1b. When the legs of a recumbent person are passively raised, the forearm blood-flow increases. This increase is due to vasodilatation since the perfusion pressure is usually unchanged and sometimes even decreased. The vasodilatation is brought

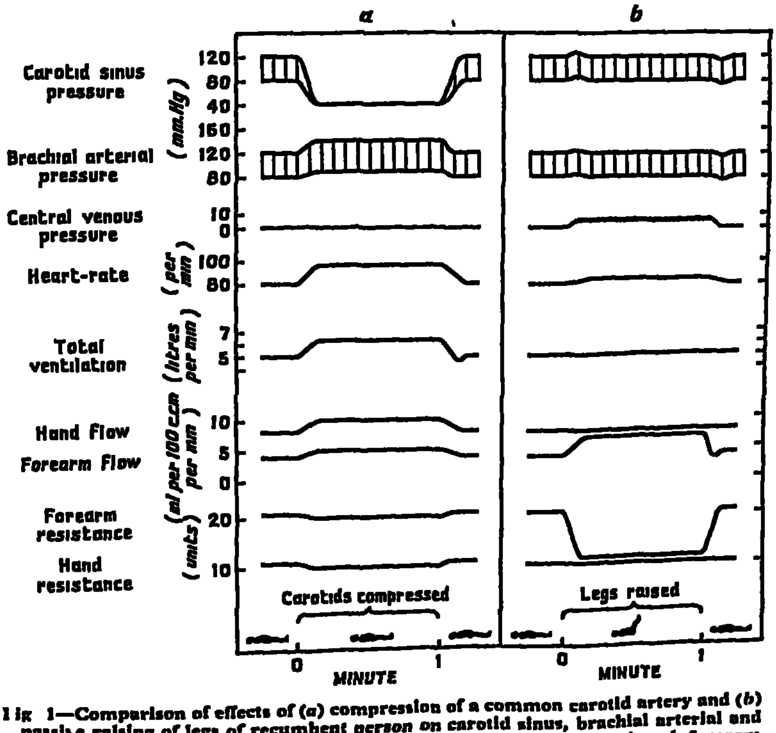

Fig 1—Comparison of effects of (a) compression of a common carotid artery and (b) passive raising of legs of recumbent person on carotid sinus, brachial arterial and central venous blood-pressure, heart-rate, total ventilation, hand and forearm blood-flow, and vascular resistance in hand and forearm

about reflexly since it is not seen in the nerve-blocked or the sympathectomised forearm (fig 2) This reflex fall in forearm vascular resistance is due to the shift of blood from the capacity vessels of the legs to the intrathoracic vascular bed since no change in resistance takes place if the return of blood from the legs is prevented by inflation of pneumatic cuffs round the thighs The shift of blood which takes place on raising the legs causes an increase in central venous pressure and in the amplitude of the venous pulsations (fig 1b) but no consistent change in either mean arterial or pulse pressure. The greater the volume of blood shifted to the intrathoracic vascular bed the bigger is the rise in venous pressure and the larger the forearm vasodilatation. Since it is impossible to correlate the changes in arterial mean or pulse pressure with the magnitude of the forearm vasodilatation this finding provides further evidence that the reflex changes in vascular resistance in the limbs that take place with change in posture are not the result of arterial baroreceptor activity but are more probably a consequence of stimulation of receptors in a low-pressure area of the intrathoracic vascular bed.

Other experiments which alter the transmural pressure in the intrathoracic vascular bed also cause reflex changes in forearm vascular resistance. During negative-pressure breathing (−15 mm. Hg), which lowers the intrathoracic pressure and thus increases the vascular transmural pressure, the forearm vascular resistance falls (Blair et al. 1958) When the receptors in the low-pressure area of the intrathoracic vascular bed are subjected to repetitive stretching brought about by rapid alternating positive and negative intrathoracic pressure changes very large falls in forearm vascular resistance are reflexly produced (Roddie et al 1958) In this way trebling or quadrupling of forearm blood-flow can be obtained

It has been shown that the stretch receptors in the carotid sinus of the cat are affected not only by changes in mean pressure but also by changes in the amplitude of the pulse-pressure transients (Ead et al. 1952) It was found that the receptors responded more to the act of stretching than to a constant stretch The present findings suggest that the same may be true for the low-pressure receptors

Efferent Vasomotor Pathway in Low-pressure Vascular Reflex

The reflex vasodilatation which takes place during stimulation of low-pressure vascular receptors is seen in the forearm but not in the hand (fig 2) Further, if the oxygen saturation of muscle and skin venous blood in the forearm is compared during such stimulation it is found that the oxygen saturation of the muscle venous blood is increased, whereas that of the skin blood is unchanged (fig 2) On the assumption that the metabolic requirements of the tissues remain unchanged the result indicates that the vasodilatation is taking place deep to the skin, presumably in muscle vessels only Therefore, though the vessels of the forearm and hand skin have a rich vasomotor innervation, they do not take part in the reflex changes caused by stimulation of the low-pressure receptors

The sympathetic fibres to skin are involved in the vasodilatation in the forearm and hand when the body temperature is raised (fig 2) The vasomotor fibres to muscle play no part in this response (Barcroft et al 1955 Edholm et al 1956a, Roddie et al 1956) Though in the hand present evidence suggests that the vasodilatation with body heating is brought about solely by release of vasoconstrictor tone (Arnott and Macfie 1948, Gaskell 1956, Roddie et al 1957f), that in the forearm skin is predominantly due to the cholinergic sympathetic nerves, whose activity causes vasodilatation (Edholm et al 1956b, Roddie et al 1957e) There is evidence, however, that the vasodilatation in forearm skin with body heating may be the result of secretomotor rather than of true vasodilator nervous activity (Fox and Hilton 1956, 1957) These workers suggest that during sweat-gland activity a bradykinin-forming enzyme is produced in skin, and that the resultant formation of bradykinin (a polypeptide with vasodilator properties) contributes to the vasodilatation in skin during body heating

The blood-vessels of human skeletal muscle are supplied with vasoconstrictor nerves (Barcroft et al 1943 Roddie et al. 1957c), and there is evidence that they also have a vasodilator nerve-supply (Barcroft et al 1944) However the vasodilatation that can be obtained with low-pressure receptor stimulation is not greater than that produced by full release of vasoconstrictor tone produced by nerve block (fig 2) Further, since blocking the activity of cholinergic vasodilator fibres in the forearm with atropine is without effect on the reflex changes (Roddie et al 1957a) probably the changes in *muscle-vessel* calibre resulting from low-presure receptor activity are brought about by alterations in vasoconstrictor tone

Discussion

The interrelationships of all the receptor mechanisms concerned in the reflex regulation of the circulation are complex, and the individual components which go to make up the final responses are difficult to analyse with precision. However, we can now define at least three types of reflexes, each utilising a different component of the autonomic nervous system on the efferent side, presumably by activation of different centres in the brain

(1) One of these centres receives impulses from the low-pressure vascular receptors and causes changes in vascular resistance in skeletal muscle.

(2) A second centre receives impulses from the arterial baroreceptors and causes changes in blood-pressure and heart-rate but does not affect resistance to blood-flow in muscle or skin.

(3) A temperature-regulating vasomotor centre which utilises vasomotor fibres to skin only

Conditions which lead to changes in cardiac output—e g , exercise and postural change—are normally associated with changes in venous return and hence the degree of stretch of the vascular walls on the right side of the heart. An increase in cardiac output in these conditions without change in peripheral resistance would raise the arterial blood-pressure This would lead not only to a large increase in the cardiac work but also to a reflex slowing of the heart due to stimulation of the arterial baroreceptors (Marey's law) Thus the receptors in the low-pressure side of the circulation would allow a large increase in cardiac output without a large increase in cardiac work and without reflex bradycardia

A sudden increase in blood volume also increases cardiac output (McMichael and Sharpey-Schafer 1944) Possibly the receptors in the low-pressure area allow this increase to take place without much change in arterial pressure the increase in venous return causing peripheral vasodilatation This type of stimulus also causes a diuresis, and there is evidence that the receptors responsible for this also lie in the low-pressure area, probably in the walls of the left atrium (Henry et al 1956a) It is likely that both the circulatory and renal responses are concerned in the normal adaptations of the body to increased blood volume It has often been suggested that vasomotor regulation of the capacity blood-vessels must play a part in the adaptation of the circulation to changes in blood volume, but evidence is accumulating that normally there is little nervous control of the capacity system in human limbs (Greenfield and Patterson 1956, Coles and Patterson 1957, Coles et al 1957)

There are numerous accounts of nervous reflex activity in isolated venous segments (Duggan et al 1953, Burch and Murtadha 1956) However, this type of result does not imply that total vascular capacity can be adjusted reflexly to any significant extent For example, it has been claimed that isolated venous segments show strong reflex vasoconstriction when the blood-pressure is lowered at the carotid sinus (Salzman 1957) However, the pressor response to carotid-artery compression *in man* is not accompanied by any increase in central venous pressure, nor is there any reduction of the total amount of blood contained in the limbs (Roddie and Shepherd 1957) This suggests that, as a whole, the capacity system was not showing any significant response to this type of stimulus

The precise location of the low-pressure receptors in the intrathoracic vascular bed concerned with reflex regulation of vasomotor tone in muscle is not known, nor is the exact nature of the stimulus Though most stimuli which cause reflex peripheral vasodilatation are associated with an increase *in* the transmural pressure in the low-pressure vascular components (e g, feet-up tilt and negative pressure breathing) they also increase amplitude of the venous pulsations caused by the cardiac cycle (Henry et al 1956b, Roddie et al 1957a) Therefore repeated acts of stretching of these receptors by pulsations may be a more effective stimulus than is a single constant stretch This suggestion is supported by the fact that a very large peripheral vasodilatation is caused by alternate positive and negative changes in intrathoracic pressure With this stimulus the low-pressure system is subjected to repeated very large artificial pulsations, but the mean transmural pressure is little altered (Roddie et al 1958) It has also been shown that a greater diuresis can be obtained in a healthy person with pulsatile changes in intrathoracic pressure than with a steady change of intrathoracic pressure of similar magnitude (Love et al 1957)

In congestive cardiac failure the transmural pressure in the low-pressure system is greatly increased, yet a further increase, brought about by postural change, does not cause peripheral vasodilatation, in fact peripheral vasoconstriction is the usual finding (Brigden and Sharpey-Schafer 1950) Furthermore, congestive failure is usually associated with a decrease in urinary output rather than an increase Perhaps pulsatile pressure-changes in the low-pressure system cause less deformation of the receptors when the vessels are grossly engorged and distended with blood than do similar pressure-changes when the vessels are only moderately full If this were so it might partly explain the anomalous circulatory reflexes and the antidiuresis commonly seen in congestive failure However, it is clear that the manner in which these receptors are stimulated is complex and cannot be explained by transmural pressure-changes alone

It is somewhat surprising, in view of the central place that the arterial baroreceptors have held in cardiovascular regulation, that the contribution of cardiac-output and peripheral-resistance changes to the changes in blood-pressure with arterial baroreceptor stimulation is, both in man and in animals, still a matter of controversy (Charlier and Philippot 1947, Kenney et al 1951, Aviado and Schmidt 1955, Brind et al *1956*) Vasoconstriction in the less vital vascular beds, such as the splanchnic area, may result from changes in arterial baroreceptor activity, but this is not so in the limbs Decreased activity of these receptors does not therefore divert blood from the limbs to the more vital structures It is clear, however, that a fall in arterial blood-pressure reflexly stimulates the heart, and perhaps the chief function of this is to increase cardiac output when the output begins to fall dangerously

Summary

Evidence is presented which demonstrates the importance of the receptors in the low-pressure vascular system in the reflex regulation of the circulation in man

Alterations in the activity of these receptors causes changes in the amount of vasoconstrictor tone in blood-vessels supplying skeletal muscles

By reflexly reducing resistance to blood-flow through skeletal muscles in this way, large increases in cardiac output can take place without a large rise in arterial pressure and hence without the large increase in cardiac work which would otherwise result

Preliminary experiments suggest that repeated stretching of these receptors may be a more effective stimulus than is a constant stretch

Changes in the activity of carotid-sinus stretch receptors cause reflex changes in blood-pressure and heart-rate but do not affect resistance to blood-flow in muscle or skin

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CHLORPHENIRAMINE MALEATE IN PROPHYLAXIS OF PYREXIAL REACTIONS DURING BLOOD-TRANSFUSIONS

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THE use of anti-histamines in the prophylaxis of pyrogenic reactions to blood-transfusion has recently received considerable attention Many workers have offered evidence that anti-histamines were effective in this respect (Ferris et al 1952, Frankel and Weidner 1953, Offenkrantz et al 1953, Simon and Eckman 1954, Stephen et al 1955) The opposite conclusion, however, was reached by Winter and Taplin (1954), and Wilhelm et al (1955)

It was therefore decided to conduct a controlled trial at the Middlesex Hospital with 200 blood-transfusions In 100 of these transfusions the blood contained an anti-histamine The incidence of pyrogenic reactions in each group was assessed

Choice of Anti-histamine

Chlorpheniramine maleate ('Chlor-trimeton' in the U S A, 'Piriton' in Great Britain) was selected Reference to the literature suggests that it is a powerful anti-histamine with few side-effects (Bernstein and Klotz 1952), and that the small dose of 10 mg in each bottle of blood is adequate (Frankel and Weidner 1953, Offenkrantz et al 1953, Simon and Eckman 1954, Winter et al 1954, Loew 1950, Wright 1950) Ferris et al (1952) were unable to confirm Baratta's (1950) impression that oral or subcutaneous administration was effective, and advised adding the material to the blood Offenkrantz et al (1953) showed that the mixture of blood and chlorpheniramine is stable

TABLE I—ANALYSIS OF PATIENTS IN CONTROLS AND PIRITON SERIES

	Controls	Piriton
No of patients	61	65
No of patients in each age-group (yr)		
15–29	4	4
30–44	13	16
45–59	20	16
60–80	24	29
ABO and rhesus blood-group		
O Rh+	27	24
A Rh+	20	20
B Rh+	3	6
AB Rh+	2	2
O Rh−	4	6
A Rh−	5	5
B Rh−	0	2
AB Rh−	0	0
Sex		
Male	29 (*48%*)	37 (*57%*)
Female	32 (*52%*)	28 (*43%*)

Plan of Trial

The scope of the trial was limited by the consideration that only one person should be responsible for adding chlorpheniramine to the blood and for the assessment of every case To ensure as wide a cross-section of patients as possible, the trial was applied to patients from three medical and two surgical wards and to the department of radiotherapy

An entirely objective assessment of whether or not a pyrogenic reaction took place was considered essential, and thus assessment was based on half-hourly oral temperatures starting before transfusion and continuing till two hours after the completion of the transfusion or until any pyrexia had regressed (Mollison 1951)

All patients receiving transfusions in the selected wards were included in the trial, except where the following contraindications applied

(1) Pre-transfusion temperature above 99 4°F
(2) Age less than 15 or more than 80
(3) Physical condition too poor to justify the burden of half-hourly temperature readings
(4) Abnormal mental condition with impaired cooperation
(5) Urgency of the transfusion
(6) Within twenty-four hours of an operation

TABLE II—DISTRIBUTION OF PATIENTS IN TWO SERIES BY ABO BLOOD-GROUP COMPARED WITH GENERAL POPULATION

ABO Blood-group	Incidence (%)		
	Controls	Piriton	Figures for general population of Britain (Dobson and Ikin 1946)
O	51	46	46 68
A	41	39	41 72
B	5	12	8 56
AB	3	3	3·04

From the actual figures of incidence of the blood-groups given in table I and from the expected values calculated from Dobson and Ikin's figures (amalgamating B–AB to avoid very low figures) $\chi^2 = 1\ 76$, $n = 4$, and $0{\cdot}80 > P > 0\ 70$

Allocation to control and piriton groups was alternate, except that multiple transfusions of the same patient were allotted alternately to either group

The following data were collected

Hospital number, name, age, and sex Diagnosis, and a clinical summary including reason for transfusion Past transfusion history, especially as regards reactions of any kind Past history of allergy Hæmoglobin concentrations before and after each transfusion, and the ABO blood-group and rhesus factor of recipient and donor (the blood-groups being identical except in one transfusion)

On the temperature chart was marked the time at which each bottle was begun and finished, the date of origin and identification number of the bottle, and any comment of the nurses about symptoms and signs of "reaction" during the transfusion No attempt was made to divide reactions into those with and those without rigor, because Mollison (1951) has pointed out that rigor may depend on external factors Instead, an arbitrary division was made into three groups as follows

(1) Temperature reaches 100°F but not 101°F
(2) Temperature reaches 101°F but not 103°F
(3) Temperature reaches or exceeds 103°

All the patients were asked by me about symptoms during the transfusion, with special reference to those that might have been either side-effects of chlorpheniramine or due to pyrexia

The resultant data, in so far as they are relevant to this article, are analysed below

TABLE III—MULTIPLE TRANSFUSIONS

No of transfusions	No of patients who had more than one transfusion in either series	
	Controls	Piriton
2	10	11
3	5	5
4	2	3
5	1	0
6	0	1
7	0	0
8	0	0
9	1	0
Total	57	55

TABLE IV—ANALYSIS OF TRANSFUSIONS IN CONTROLS AND PIRITON SERIES

	Controls	Piriton
Average no of bottles per transfusion	2·43	2·49
ABO and rhesus blood-group of patient in each transfusion		
O+	42	36
A+	29	33
B+	7	10
AB+	4	2
O−	13	10
A−	5	8
B−	0	1
AB−	0	0
Total	100	100

Results

No side-effects of chlorpheniramine were observed except moderate drowsiness in three patients

The control and treatment groups have been analysed for comparability in tables I–IV, which show that, as regards age, sex, and blood-group (table I), the groups do not significantly differ Neither series shows a distribution of blood-groups which differs significantly from that for the general population (table II) Table III presents details of multiple transfusions in each group The patterns of distribution are similar Table IV analyses the two groups as transfusions rather than as individuals, and shows an essential similarity between the two groups as regards average volume of transfusion and blood-group of the patient in each transfusion

Table V presents the incidence of pyrogenic reactions in control and treatment series Grade-3 reactions took place with almost the same frequency irrespective of whether or not the blood contained the anti-histamine Neither the small difference in incidence in the grade-1 pyrexias nor the overall incidence for all three grades is significant

Discussion

The overall incidence of transfusions associated with pyrogenic reactions was 35%, whereas the incidence-rate given in published reports is usually 3–6% There appear to be four possible reasons for this discrepancy

(1) For the assessment of the incidence of pyrogenic reactions most investigators have relied on taking a history from the patient the day after transfusion and upon the reporting by the nurses of a chill-fever reaction The present trial has shown, however, that often a patient can develop a pyrexia of 101° or 102°F without any sign to attract the attention of the nurses, and even without any symptoms to recount on direct inquiry the next day

The opposite discrepancy, though much less common, was also observed A few patients claimed to have " felt feverish " during the transfusion, though their temperature never reached 100°F

(2) Some of these pyrexias will have been coincident with, but not caused by, the blood-transfusion No effort was made to exclude from the trial any patient who, because of his complaint, would be likely to develop a temperature, so long as he was apyrexial at the start of the transfusion Degrees of liability to have pyrexia would have been difficult to assess and to control However, most published reports do not mention that such patients have been excluded, so this factor is unlikely to be a major cause of the discrepancy

TABLE V—INCIDENCE OF PYROGENIC REACTIONS

Grade of pyrexial response	No of pyrogenic reactions in groups according to maximum temperature	
	Controls	Piriton
1, reaching 100°F but not 101°F	23	17
2, reaching 101°F but not 103°F	10	9
3, reaching or exceeding 103°F	5	6
Total	38	32

Difference in total incidence = 6% Standard error of the difference = 6·73%
For the grade-1 responses
Difference in incidence = 6% Standard error of the difference = 5·61%
Neither difference is statistically significant

(3) In all grade-2 and grade-3 reactions hæmolysis due to blood-group incompatibility was excluded by the appropriate investigations

(4) An excessive incidence of pyrogens in the transfusion apparatus was unlikely because the thermal reactions were evenly spread over the twelve months of the trial, and because no case of pyrexia associated with electrolyte infusion alone was reported to me during this time

If a true incidence of pyrexia during transfusion of 35% has been assessed by previous investigators at 5%, it is not surprising that the apparent efficacy of any agent in reducing the incidence varies widely from series to series Moreover, no published reports include an analysis of their control and treatment groups for comparability Particularly important in this connection is the factor of multiple transfusions One or other group may by chance be loaded with a few patients specially susceptible to pyrexia, either because of their illness or because they are sensitive to transfused blood (Dameshek and Neber 1950) This source of error has in the present series been controlled by the method of allocation, and table III suggests that the method was efficacious

The results of this trial indicate that there is no justification for the routine prophylactic use of an anti-histamine in each bottle of transfused blood in an effort to prevent pyrogenic reactions Even if the 6% (38–32%) difference between control and treatment groups for grade-1 reactions were repeated in a larger series and so became statistically significant, this would still not be an argument in favour of routine anti-histamine medication of the blood The addition of any material to a bottle of blood must carry with it some danger of contamination, and this consideration would outweigh the avoidance of 6 minor thermal reactions in every 100 transfusions

These conclusions do not apply in the particular instance of patients with a known history of allergy Published reports agree that such patients are particularly liable to allergic reactions to blood-transfusion (e g, Maunsell 1944), and that prophylactic anti-histamine medication of the blood reduces the incidence of allergic reactions almost to zero (Hoffman 1957) My experience is similar, and it is my custom to endeavour, where possible, to elicit a history of allergy in all patients about to be transfused Where the history is positive, chlorpheniramine 10 mg is added to each pint of blood

Summary

A controlled trial was made to test the efficacy of an anti-histamine, chlorpheniramine maleate, in preventing pyrexial reactions during blood-transfusion

No statistical evidence of such an effect was obtained

This conclusion does not affect the validity of the practice of using chlorpheniramine 10 mg, in each bottle of blood for transfusion to all patients with a history of allergy, so as to reduce the incidence of allergic reactions

My thanks are due to the blood-transfusion subcommittee of the Middlesex Hospital for permission to conduct this trial, and to Dr J W Stewart, of the Bland-Sutton Institute of Pathology, for valuable technical assistance The ' Piriton ' was supplied by Messrs Allen and Hanburys, Ltd

References at foot of next column

PSYCHOSIS AND TREMOR DUE TO MECAMYLAMINE

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MECAMYLAMINE as a ganglion-blocking agent for treating hypertension was introduced two years ago (Freis 1955, Ford et al 1955), and since then it has been widely used in clinical practice, its chief advantage being that it is fully and regularly absorbed when given by mouth It produces the same side-effects, due to blockade of the parasympathetic system, as do other ganglion-blocking drugs, but in addition reports have been published in America indicating that mecamylamine may also have a toxic action on the central nervous system (Schneckloth et al, 1956, Deming et al 1957)

We describe here four patients in whom tremor and mental disturbance, with confusion and hallucinations, developed while they were receiving mecamylamine, and we suggest that this may be a not uncommon complication of treatment with mecamylamine given in large dosage

Case-reports

Case 1 —A man, aged 55, was first seen in July, 1955, complaining of headaches He had two years' history of high blood-pressure and fifteen years' history of gout Although intelligent, he was unstable and did not follow any regular occupation

On examination his blood-pressure was 230/140 mm Hg, he had numerous retinal hæmorrhages and exudates, his urine contained a trace of albumin and could be concentrated to 1 020, and his blood-urea level was 30 mg per 100 ml

Treatment —Benign essential hypertension having been diagnosed, he was treated with subcutaneous pentolinium, to which reserpine 0 1 mg thrice daily was later added This regime reduced his blood-pressure, and his fundi considerably improved

Mecamylamine therapy —In July, 1956, mecamylamine was substituted for the pentolinium, 20 mg thrice daily being necessary to keep the blood-pressure down to 140 80 mm Hg, with the patient in the erect position, for the greater part of the day This dosage, however, caused troublesome side-effects, at first principally constipation, but later difficulty in micturition associated with frequency

Readmission —In February, 1957, retention of urine developed and the patient was readmitted to hospital His blood-urea level was now 60 mg per 100 ml, rising after ten days to 72 mg per 100 ml, he had a urinary infection, which was treated with tetracycline Soon after admission his requirement for mecamylamine fell the dosage was reduced from 60 to 30 mg daily, and his blood-pressure was maintained at 110/70 mm Hg with the patient in the upright position

Mental and nervous symptoms —On Feb 19, 1957, he had a tremor of the hands All hypotensive treatment was stopped, but next day the tremor had increased and he became mentally confused Two days later his condition had deteriorated further he had a coarse generalised shaking affecting his whole body, present at rest, and accentuated on attempting any voluntary movement His speech was slurred and jerky There was a general increase in muscular tone and in the deep reflexes, the plantar responses remained flexor He was completely disoriented in both space and time and had vivid frightening hallucinations His extreme restlessness and picking at the bedclothes suggested alcoholic delirium tremens From time to time he had lucid intervals during which he had considerable insight into his condition Repeated large oral doses (10–15 ml) of paraldehyde subdued the tremor and relieved the hallucinations for three to four hours at a time

This striking clinical picture persisted for a week and then gradually subsided By March, twelve days after the mecamylamine treatment had been stopped, the hallucinations had disappeared and the patient's mental state had returned to normal He could now remember in detail what had happened during his delirium Slight tremor persisted for a further two days before finally clearing During this period he had been treated with subcutaneous pentolinium because his blood-pressure had risen after the cessation of hypotensive therapy, but it was difficult to keep his blood-pressure down, because he was confined to bed He was discharged from hospital on March 14, 1957, taking two injections of pentolinium daily, his blood-urea level had fallen to 38 mg per 100 ml

Readmission —Four months later he was readmitted with uræmia and left ventricular failure and died in five days

Necropsy

There was atheroma of the blood-vessels at the base of the brain, the gyri were flattened, but no localised abnormality was found on section of the brain The kidneys showed lesions of malignant nephrosclerosis

Case 2 —A woman, aged 65, was admitted to hospital in July, 1956, with left ventricular failure She had eight weeks' history of exertional dyspnœa Her blood-pressure was 300/160 mm Hg, and she had hæmorrhages and soft exudates in her fundi Her blood-urea level was 30 mg per 100 ml She was treated with digitalis, mersalyl, and hypotensives—at first subcutaneous pentolinium and later oral mecamylamine When first seen at Hammersmith Hospital in September, 1956 she was very much improved symptomatically, but her blood-pressure was 200/130 mm Hg, and the dosage of mecamylamine was increased from 12 5 to 20 mg twice daily In October the dosage was further increased to 45 mg daily, but, although this dosage did not control the hypertension, urinary retention developed and she was admitted to hospital on Oct 29, 1956

On admission she was cooperative and well oriented but somewhat apprehensive and overexcitable Her blood-pressure was 290 140 mm Hg, and soft exudates but no papillœdema were noted in her fundi There was no sign of heart-failure Her urine contained albumin, and her blood-urea level was 66 mg per 100 ml Mecamylamine therapy was continued, the dosage being slowly increased until on Nov 6, 1956, she was having 65 mg daily Her systolic blood-pressure remained about 200 mm Hg

Mental and nervous symptoms —In the early hours of Nov 11 1956, she became agitated and confused, having hallucinations of voices and complaining of noises in the head Her blood-pressure was 170 90 mm Hg She had general hyperreflexia

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During the succeeding days her confusion increased, and she was disoriented for most of the time but had intervals of insight and cooperation Mecamylamine therapy was stopped on Nov 13 On Nov 17 she was grossly confused and hallucinated, with paranoid delusions She also had a coarse tremor of arms and legs Her blood-urea level had risen to 97 mg per 100 ml on Nov 17 and to 140 mg per 100 ml on Nov 20 She became more agitated and violent and was completely inaccessible On Nov 21 her condition made it necessary to transfer her to a mental observation ward She went progressively downhill, her blood-urea level rose to 296 mg per 100 ml, and she died on Nov 30, 1956, without any improvement in her mental state

Necropsy

The left kidney was small (55 g) with generalised ischæmic atrophy suggesting occlusion of the renal artery The right kidney weighed 110 g, and its histology was that of florid malignant nephrosclerosis The brain showed a small area of softening in the right internal capsule, and the cerebral arteries were considerably affected by atheroma

Case 3—An electrical engineer, aged 53, was found in January, 1956, to have a blood-pressure of 240/140 mm Hg, bilateral papillœdema, heavy albuminuria, and a blood-urea level of 40 mg per 100 ml Malignant essential hypertension was diagnosed, and he was treated with subcutaneous pentolinium and with rauwolfia alkaloids, but his blood-pressure was difficult to control, and during the next six months further deterioration in the fundi and increasing cardiac enlargement were noted

On admission to Hammersmith Hospital in July, 1956, he had heart-failure, blood-pressure 260/140 mm Hg, bilateral papillœdema, hæmorrhages and exudates in his fundi, and albuminuria His blood-urea level was 139 mg per 100 ml

Treatment with subcutaneous pentolinium was continued, a dosage of 30–40 mg twice daily being necessary to control his blood-pressure Rauwolfia was not given Chlorpromazine 50 mg thrice daily was given because of vomiting After a month the heart-failure had cleared and the blood-urea level fallen to 60 mg per 100 ml

Mecamylamine therapy—On Sept 10, 1956, mecamylamine therapy was started, and pentolinium was withdrawn gradually during the next few days The blood-pressure was not satisfactorily controlled during the period of transfer, but by Sept 17 it was down to 140/80 mm Hg, with the patient in the erect position, for most of the day This was achieved with a dosage of 20 mg mecamylamine thrice daily By now the blood-urea level had risen again to 100 mg per 100 ml The fundi still showed papillœdema, but there were no fresh exudates or hæmorrhages

Mental and nervous symptoms—On Sept 24, 1956, shaking of the limbs and trunk was first noted This tremor also affected the face and tongue, it was coarse and present at rest but exaggerated on voluntary movement The speech was jerky and difficult to understand There was a general increase in muscular tone, the tendon-reflexes were exaggerated, and knee and ankle clonus could be elicited, the plantar responses were flexor Mecamylamine was withheld after it had been taken for fourteen days, and pentolinium therapy was restarted, but the tremor increased, and four days later the patient became drowsy and confused He was now disoriented and hallucinated, speaking to imaginary people and seeing snakes and insects crawling across his bedclothes His body shook so violently as to rock the whole bed Paraldehyde reduced the tremor somewhat, but he remained confused and steadily deteriorated His blood-urea level rose to 170 mg per 100 ml, his urinary output fell, and he died, after repeated attacks of left ventricular failure, on Oct 7, 1956

Necropsy

The brain was overweight (1490 g) and œdematous, with a small area of recent softening at the posterior end of the putamen on each side and a recent small hæmorrhage in the mid-pons The kidneys were typical of malignant nephrosclerosis

Case 4—An electrician's mate, aged 46, presented in January, 1956, with four months' history of blurring of vision and dyspnœa His blood-pressure was 250/150 mm Hg and he had bilateral papillœdema with scattered retinal hæmorrhages His urine contained albumin, granular casts, and occasional leucocytes, his blood-urea level was 155 mg per 100 ml There was no history to suggest previous renal disease In view of his visual symptoms hypotensive therapy was considered advisable, in spite of the severe renal failure, and treatment was started with subcutaneous pentolinium At the end of February his blood-urea level was 222 mg per 100 ml

Mecamylamine therapy—At this stage he was given oral mecamylamine He was not very sensitive to it, 60 mg in divided doses daily being needed to keep his blood-pressure down to 160/100 mm Hg On April 14, 1956, six weeks after mecamylamine therapy had been started, he was readmitted to hospital with increasing trembling of his arms and legs for the previous three days On admission his blood-pressure was 160/90 mm Hg He still had bilateral papillœdema He was dyspnœic, and his jugular venous pressure was raised

Mental and nervous symptoms—He was drowsy and mentally confused He had occasional spontaneous quivering of his lips and a coarse irregular tremor of his limbs His muscular tone was increased, his lower limbs showed almost cogwheel rigidity His tendon-reflexes were uniformly increased, and he had bilateral ankle clonus His plantar responses were flexor Hypotensive therapy was stopped, and he was treated only with digoxin, but the confusion and tremor persisted, and he died on April 16, 1956

Necropsy

The kidneys showed the changes of malignant nephrosclerosis The brain showed cerebral œdema, but no localised lesion or other abnormality

Discussion

The clinical picture was similar in each of these four patients In three the first neurological abnormality to be noted was a coarse tremor which affected the trunk and head as well as the limbs and caused difficulty with speech It was variable in the early stages, perhaps hardly noticeable when a limb was at rest, but brought out when voluntary movement was attempted The shaking of the trunk made it look as if the patient was *shivering* The tremor was equally present on both sides of the body At its height it was so violent in two patients as to shake the whole bed Mental symptoms were observed before the tremor in one patient, but in the others a few days after the tremor They consisted of a clouding of consciousness with confusion and disorientation, together, in three cases, with hallucinations which were usually visual but sometimes also of hearing or of touch The mental state fluctuated, and there were lucid intervals, with some insight, between periods of extreme delirium Both tremor and mental symptoms were alleviated temporarily by administration of paraldehyde, in case 1 strikingly so In this patient, who recovered from the episode, the mental abnormalities disappeared first, the tremor persisting for a few days before finally clearing

Examination of the nervous system in these patients revealed a general increase in muscle tone, symmetrically exaggerated tendon-reflexes with clonus, and flexor plantar responses In no case were any lateralising signs found Electroencephalography in three cases gave records which were difficult to interpret because of artefact due to muscle tremor, there was complete absence of alpha rhythm, but in no case was positive evidence found either of a general metabolic disturbance or of a localised lesion

The patients all had severe hypertension In two this was frankly malignant, with papillœdema, in the other two the presence of active retinitis and progressive renal failure indicated that the hypertension was in a premalignant phase, and at necropsy lesions of malignant nephrosclerosis were found in the kidneys Renal function was impaired in all In three there was gross renal failure with a raised blood-urea level which continued to rise until death, in case 1, who already had some renal impairment shown by a failure of concentrating power, but who had a normal blood-urea level, there was a further deterioration in renal function and a temporary rise in the blood-urea level coincident with a urinary infection This patient's blood-urea level had returned to normal by the time that his neurological symptoms had cleared, but it rose again later, and uræmia was present at his death four months afterwards

All four patients were receiving large dosages of mecamylamine (60–65 mg daily) because smaller amounts had not reduced the blood-pressure The duration of administration of mecamylamine before neurological symptoms developed varied from seven months in case 1 to fourteen days in case 3 Case 1 had the least impairment of renal function

Since cerebral arterial disease is common in hypertensive patients, the question arises whether organic brain damage due to hæmorrhage or to infarction could have caused the symptoms observed Evidence of local cerebral lesions was found at necropsy in two cases in the right internal capsule in one case, and in both basal ganglia and the pons in the other The whole clinical picture, however, was more like a toxic confusional reaction, bearing in its fully developed state a striking resemblance to alcoholic delirium tremens The symmetry of the tremor, the absence of any lateralising signs in the central nervous system, and particularly the complete disappearance of symptoms in case 1 after mecamylamine had been withheld suggest strongly that this drug was to blame In the patients who did not recover, uræmia and death supervened probably before sufficient time had elapsed to allow the mecamylamine to be cleared from the body

Mecamylamine is a secondary amine and freely diffusible across cell membranes There is evidence that this drug is concentrated within the cell (Milne et al 1957) It is therefore likely that its mode of action differs from that of ganglion-blocking agents such as hexamethonium and pentolinium, which are quaternary ammonium compounds and are distributed only in the extracellular fluid That mecamylamine has a different, and previously unrecognised, mode of action at the neuromuscular junction has been shown by Bennett et al (1957) From this it might also be expected that mecamylamine, apart from producing the same side-effects due to parasympathetic blockade as other ganglion-blocking drugs, might also have toxic actions from which methonium compounds are strikingly free There is some experimental evidence of a direct toxic action on the central nervous system Rats given mecamylamine in large doses develop a tremor and have generalised convulsions before death (Milne et al 1957)

The frequency of this complication of treatment is not certain Doyle et al (1956), Smirk and McQueen (1957) and Kitchin et al (1957), in their accounts of clinical experience with mecamylamine, do not mention any neurological symptoms related to its administration The four cases described here occurred among ninety patients treated with mecamylamine at this hospital (twenty of them with malignant hypertension) The average daily dosage of mecamylamine in the whole series, however, was only 35 mg, and only sixteen patients received more than 50 mg daily Moreover, this is a selected group of patients, including some with severe hypertension who were specially referred

In addition to the cases described in detail above, three other patients treated with mecamylamine developed a tremor without mental symptoms a woman, aged 31, with malignant hypertension and systemic lupus erythematosus and a woman, aged 51, with malignant hypertension and renal-vein thrombosis, both with moderate impairment of renal function (blood-urea level 40–70 mg per 100 ml), and a man, aged 51, with malignant essential hypertension and uræmia (blood-urea level 114 mg per 100 ml) The daily dosage of mecamylamine in these patients was 25, 50, and 30 mg respectively In the two women the tremor disappeared when the dosage of mecamylamine was reduced and pentolinium was partly or wholly substituted It certainly seems that patients with severely impaired renal function are much more likely to develop symptoms of neurotoxicity while taking mecamylamine of five patients in whom the blood-urea level was 100 mg per 100 ml or higher at the start of treatment four developed tremor and three of these mental symptoms This complication is presumably related to the retention of mecamylamine in the body, its urinary excretion being reduced in renal failure (Milne et al 1957)

Summary

Four cases are described in which a syndrome of tremor, mental confusion, and delirium developed under treatment with mecamylamine Tremor developed in three other patients

This complication of mecamylamine treatment occurred in patients receiving large dosages thereof (60–65 mg daily), all these patients had or subsequently developed malignant hypertension and in all renal function was impaired

We thank Prof J McMichael and Dr M D Milne for their help and advice, and Dr J F Goodwin for permission to report a patient under his care

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"How then does a good physician help a patient to face death and, accepting the ways of nature, to meet it? It is not done by all the busy paraphernalia of scientific medicine, keeping a vague shadow of life flickering when all hope is gone If man lives as a stranger in a lonely crowd, he dies utterly alone Whereas his entry into the world is the first stage of the dissolution of an intimate partnership with his mother, his final departure is the ultimate in solitary procedures"—WILLIAM B BEAN, *Arch intern Med* 1958, 101, 201

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Papers

ESSENTIAL FATTY ACIDS AND IDIOPATHIC HYPERCALCÆMIA OF INFANCY

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ATTENTION has been drawn to the possible role of a deficiency of "essential" fatty acids (linoleic and arachidonic acids) in the genesis of idiopathic hypercalcæmia of infancy (*Lancet* 1957) It has been suggested (Sinclair 1956a) that in the preparation of evaporated milks there is some loss of essential fatty acids and an even greater loss in the production of National Dried Milk made by passage over hot rollers, thus infants fed on dried milk preparations might receive a diet deficient in essential fatty acids This suggestion could have provided an additional explanation of the frequency with which hypercalcæmia of infancy has been recognised in the United Kingdom, where dried milks are widely used, although one established factor to explain this frequency has been the extent of fortification of infant foods with vitamin D (*British Medical Journal* 1956)

We have studied the fatty-acid composition of samples of human milk, cows' milk before and after drying by a variety of commercial techniques, stored dried milk, and evaporated milk Similar analytical studies of whole blood from three healthy infants have been made, as well as from three infants with idiopathic hypercalcæmia, the latter were studied both before and after treatment with cotton-seed oil (a rich source of linoleic acid) The fatty-acid analyses were made with the gas-liquid chromatogram (James and Martin 1956)

Methods

Each sample of milk was extracted exhaustively with ether-ethanol overnight to remove the lipids Samples of whole blood were similarly extracted The lipid extracts were saponified with methanolic potassium hydroxide, and the non-saponifiable material was extracted with petroleum ether The alkaline solution was acidified with 5*N* sulphuric acid, and the fatty acids were extracted with petroleum ether The extract was dried over anhydrous sodium sulphate, and the acids were converted to methyl esters by refluxing with anhydrous methanolic hydrochloric acid Samples were stored in high dilution in petroleum-ether solution at +2°C, and the solvent was removed by evaporation before applying the sample to the gas-liquid chromatogram

Under the conditions used for the fatty-acid analyses the gas chromatogram does not differentiate between the cis-cis, cis-trans, and trans-trans forms of linoleic acid In addition linoleic and linolenic acids (the C_{18} di- and tri-unsaturated acids) are not separated, so the figures reported refer to the sum of these two acids However, the linolenic-acid content of all the fats studied is likely to be low

Studies in collaboration with other laboratories have shown excellent agreement between the gas chromatographic and spectrophotometric techniques for determining (1) a combined value for linoleic and linolenic acids and (2) arachidonic acid The linoleic acid isolated from cows' milk by the gas chromatogram has been shown to be 9 12-octadecadienoic acid by the micro degradation procedure described by James and Webb (1957)

Results

Changes in Fat-composition of Milk on Processing to Dried Milk and on Storage

In Table I are listed the linoleic-acid + linolenic-acid contents of fresh milk, the same milk after concentration, and then after roller drying of this concentrated milk No loss of these two acids was found, although the same experiment was repeated several times

Table I also shows the linoleic-acid + linolenic-acid contents of the same sample of milk after storage under various conditions After three months at room temperature or at 37°C the "essential" fatty-acid content had fallen to two-thirds of the original value, after six months' storage under similar conditions the "essential" fatty acids had dropped to less than half their previous value

Comparative Analyses of Various Milk Preparations used in Infant Feeding

Table II shows comparisons of the fatty-acid composition (major components only) of two samples of human milk, fresh cows' milk, roller-dried milk, National Dried Milk, and 'Carnation' evaporated cows'-milk The difference in the levels of linoleic + linolenic acids in human milk and cows' milk was less than has sometimes been supposed, but the effect of diet on these levels has yet to be determined

TABLE I—LINOLEIC-ACID CONTENT OF COWS' MILK DURING PROCESSING AND STORAGE (AS PERCENTAGE OF ACIDS IN THE RANGE C_6-C_{20})

—	Fresh milk 12% total solids	*Milk* concentrated before drying (21% total solids)	After roller drying	Powder stored 3 mos at room temperature	Powder stored 6 mos at room temperature	Powder stored 3 mos at 37°	Powder stored 6 mos at 37°
Linoleic acid + linolenic acid	3·2	3·0	3·4	2·3	1·4	2·4	1·1

"*Essential Fatty-acid*" *Levels in Blood of Infants with Hypercalcæmia*

Case 1—A male infant, born on Feb 21, 1956, who had well-established hypercalcæmia, was studied at the age of 9 months He was fed cotton-seed oil containing 50% w/w of linoleic acid for twenty days During the first five days he received about 5 ml of cotton-seed oil a day, during the next twelve days about 8 ml a day, and during the last three days about 20 ml a day The serum-calcium (table III and fig 1) had been high for so long that it seemed improbable that the fall from 15·8 mg per 100 ml to 9·9 mg per 100 ml in ten days was due to a chance variation in its level, although such variations are known to occur Analyses were made of the fatty acids of whole blood taken from this child before, while, and after he was given cotton-seed oil No significant change

TABLE II—MAJOR COMPONENTS OF MILK FATS FROM VARIOUS SOURCES EXPRESSED AS PERCENTAGE OF FATTY ACIDS IN RANGE C_6-C_{20}

Acid	Human milk		Cows milk			
	Sample 1, ten days after start of lactation	Sample 2, three mos after start of lactation	Fresh	'Ostermilk' roller-dried	National Dried Milk bought from a clinic	'Carnation' tinned milk
Myristic	5·7	9·0		10·7	10·6	9·4
Branched C_{15}	0·5	0·2	0·8	1·3	1·6	1·8
nC_{15}	0·8	0·4	1·0	1·3	1·2	1·4
Palmitoleic	3·9	2·6	2·2	2·2	2·0	2·4
Palmitic	26·5	20·0	26·4	29·7	16·6	21·8
Branched unsat C_{17}	1·5	0·8	1·5	1·5	2·0	1·5
nC_{17}	0·7	Trace	0·7	1·1	0·6	0·8
Linoleic	5·1	4·4	3·2	3·5	4·1	4·4
Oleic	38·6	46·0	23·3	26·1	30·4	26·0
Isomers of oleic acid	Not measured		3·6	3·1	10·0	5·1
Stearic	12·1	7·7	10·3	12·0	10·5	13·8
Poly-unsat C_{20} (not arachidonic)	1·8	Not measured			1·0	2·0

TABLE III—COMPARISON OF CHEMICAL FINDINGS IN BLOOD OF NORMAL INFANTS AND THOSE WITH HYPERCALCÆMIA

—	Date	Treatment	Serum-calcium (mg per 100 ml)	Serum-cholesterol (mg per 100 ml)	Linoleic and linolenic acids as percentage of total fatty acids	Arachidonic acid as percentage of total fatty acids
3 infants without hypercalcæmia	—	—	10 7	—	9·4	5 4
	—	—	10 6	—	10 3	4 8
	—	—	11 7	—	10 6	4 3
3 infants with hypercalcæmia						
Case 1	Nov 29, 1956		14 8	—	—	—
	Dec 6, ,,		14 5	—	—	—
	,, 17, ,,		15 8	—	8 6	3 4
	,, 20, ,,	Cotton-seed oil started				
	,, 27, ,,		9 9	—	—	—
	Jan 7, 1957		10 3	—	9 8	5 6
	,, 10, ,,	Cotton-seed oil stopped				
	,, 20, ,,		11 5	—	7 1	3 6
	,, 29, ,,		12 7	—	—	—
	Feb 5, ,,		11 6	—	—	—
	,, 12, ,,		12 2	—	9 9	4 2
Case 2	June 4, 1957		13 8	310	8 6	4 6
	,, 11, ,,	Cotton-seed oil started	14 1	—	—	—
	,, 18, ,,		12 5	257	25 8	5 1
	,, 25, ,,	Cotton-seed oil stopped	13 7	296	25 6	4 3
	July 1, ,,		14 6	287	—	—
	,, 9, ,,	Cortisone 100 mg b d started				
	,, 16, ,,		12 3	—	8 6	4 6
Case 3	Aug 23, 1957		15 4	—	—	—
	,, 27, ,,		13 2	251	9·9	4 6
	,, 29, ,,	Cotton-seed oil started				
	Sept. 4, ,,		11 2	218	22 6	4 5
	,, 11, ,,		12 2	209	28 2	5 4
	,, 13, ,,	Cotton-seed oil stopped				
	,, 17, ,,		12 1	223	—	—

occurred in the blood levels of linoleic and linolenic acids or of arachidonic acid

As a result of the observed changes in serum-calcium levels more detailed studies were made on two children with the complex type of hypercalcæmia

Case 2 —A boy, born on April 2, 1956, was studied at the age of 14 months He had the facies seen in severe hypercalcæmia, severe osteosclerosis, a raised blood-urea, and hypercholesterolæmia Between the ages of $12^1/_2$ months and 14 months he had received a moderately low-calcium diet containing no vitamin D He gained no weight in that period, and his serum-calcium and blood urea remained high (table III and fig 2) Throughout the tests reported here he was fed on homogenised cows'-milk A four-day balance study before he was given any cotton-seed oil showed an average daily positive balance of 172 mg of calcium A week after treatment with cotton-seed oil was started (about 40 ml a day in divided doses before each feed), a second four-day balance study showed an average daily negative balance of 23 mg of calcium This difference between the two balances was explained by an increase in the fæcal calcium There was no change in the urinary calcium The serum-calcium showed a transient fall after seven days simultaneously with a slight transient fall in the levels of plasma-phospholipids and total, free, and esterified cholesterol Within fourteen days these levels had all risen, and after twenty-one days' treatment with cotton-seed oil the serum-calcium was as high as it had been before the oil was given The linoleic-acid level in the whole blood rose within seven days of the start of treatment with cotton-seed oil and was still high at fourteen days

Case 3 —A girl, born on Jan 13, 1957, was studied at the age of 7 months She had a history of vomiting and constipation for some weeks She had early osteosclerosis Her serum-calcium was 15 4 mg per 100 ml and blood-urea 52 mg per 100 ml Four days later her serum-calcium level was 13 2 mg per 100 ml and serum-cholesterol 251 mg per 100 ml (table III and fig 2) After a week's treatment with cotton-seed oil 40 ml daily in divided doses before feeds, her serum-calcium was 11 2 mg per 100 ml , but after two weeks' treatment it had risen to 12 2 mg per 100 ml A slight initial gain in weight during treatment was not sustained The level of linoleic + linolenic acid was high both one and two weeks after the start of treatment with cotton-seed oil

Discussion

The results here do not support the proposition that the actual processing of cows' milk, whether by vacuum evaporation or by roller drying, causes any great fall in the level of linoleic + linolenic acids Linolenic acid can exist in three forms—cis-cis, cis-trans, and trans-trans—but only the cis-cis form can be utilised Van Beers et al (1957) have shown that about 50% of the linoleic acids of cows' milk is in the cis-cis form, so it cannot be claimed that infants fed on cows' milk are being provided solely with the wrong stereoisomer Furthermore there is no chemical reason to expect rearrangement of the cis-cis linoleic acid during drying

The level of linoleic + linolenic acids did, however, fall on prolonged storage of dried milks, as previously stated by Sinclair (1956b), but we have no evidence at present to suggest that the levels observed lead to any deficiency

The blood levels of linoleic + linolenic acids and arachi-

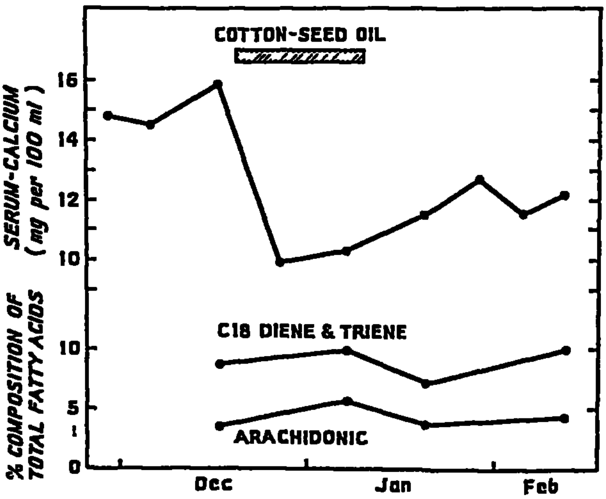

Fig 1—Case 1

donic acid were similar in three normal infants to those found in three infants with hypercalcæmia

The fact that the amounts of arachidonic acid fall within the normal range precludes any suggestion that the combined level of linoleic and linolenic acids conceals a lowered linoleic level and an enhanced linolenic level, since it is known that cis-cis linoleic acid is the precursor of arachidonic acid

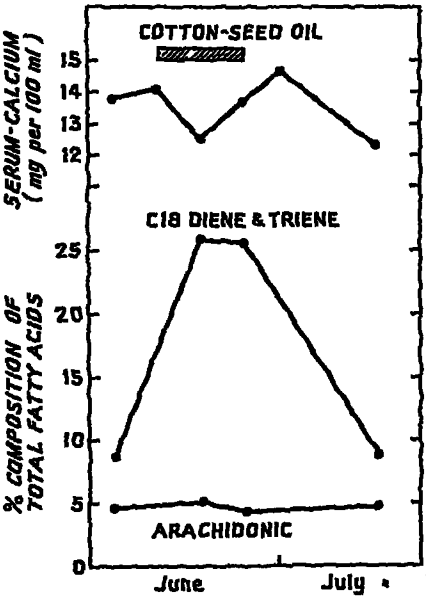

Fig 2—Case 2

A transient fall in the serum-calcium occurred in all three infants when given cotton-seed oil by mouth, this was probably due to an increased excretion of calcium in the fæces, shown by balance studies in case 2 Although the linoleic+linolenic-acid levels in the blood rose in two cases, the serum-calcium rose again while the fatty-acid levels were still high (table III and figs 2 and 3)

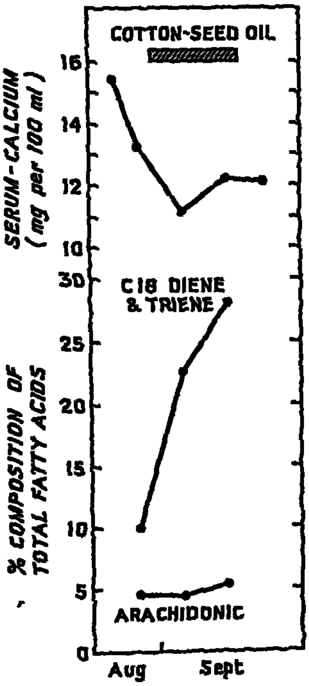

Fig 3—Case 3

It is impossible, on the available evidence, to say whether or not there is any association between the changes in the serum-cholesterol and serum-calcium levels

These results do not provide any evidence that an essential fatty-acid deficiency is a cause of, or is present in, infants with idiopathic hypercalcæmia

We wish to thank Dr W F J Cuthbertson, of Glaxo Laboratories Limited, for providing the samples of roller-dried and freeze-dried milk, Dr Andrew Barlow for referring case 2, Dr K J Kingsbury and Dr V H T James for the serum-cholesterol determinations, and Mr H Hadaway and Mr I W J Evans for much technical assistance

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SEPTICÆMIA IN MODERN THERAPY

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8 CASES of septicæmia in surgical patients, all within ten months, are reported here to illustrate the increasing incidence of serious infections associated on the one hand with the emergence of the resistant hospital staphylococcus, and on the other with corticosteroid therapy

Case-reports

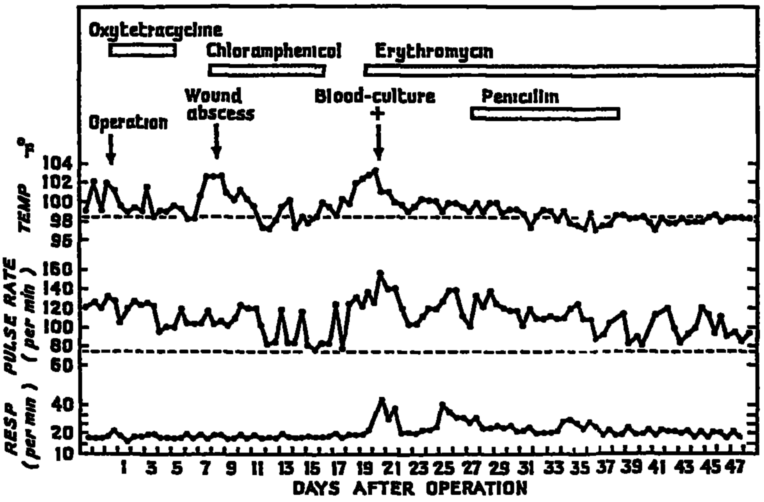
Case 1—A man, aged 44, was admitted with severe ulcerative colitis Failure of cortisone (150 mg per day for six weeks) necessitated colectomy and ileostomy as an emergency measure under corticosteroid cover to prevent collapse (Slaney and Brooke 1957) Eight days later he developed a wound abscess, containing *Staphylococcus pyogenes* sensitive only to chloramphenicol and erythromycin, chloramphenicol was administered After a further ten days when the patient was again gravely ill (see figure), blood-culture demonstrated a heavy growth of *Staph pyogenes*, with similar resistance The same organism was also isolated from sputum, urine, the site of an abdominal drainage tube, the distal sigmoid colostomy, and a subcutaneous abscess on the arm X rays revealed metastatic abscesses in the lungs, which gradually disappeared as the patient's condition responded to erythromycin (2 g daily) over the next six weeks Penicillin 20 million units daily, despite insensitivity to this drug, was added to erythromycin for its possible synergic effect The patient recovered

Case 2—A man, aged 40, with ulcerative colitis, underwent primary colectomy under cortisone cover following steroid therapy Eight days later the patient's pulse-rate rose to 130 and the temperature to 103°F, though he felt well Blood-culture revealed septicæmia due to *Clostridium welchii* and *Diplococcus mucosus* Both organisms were sensitive to chloramphenicol, which was given for five days, followed by erythromycin for twelve days He recovered

Case 3—Colectomy and rectal anastomosis were performed in a man, aged 33, on account of extensive Crohn's disease of the colon, corticosteroid cover being given since he had previously received steroid therapy A week later peritonitis developed, laparotomy revealed disruption of the suture line necessitating closure of the rectal stump and the establishment of an ileostomy Eight days after this second operation the temperature rose to 103°F and the pulse-rate to 140, an erythematous rash appeared on the face and neck and became purpuric the following day *Staph pyogenes* resistant to all antibiotics except chloramphenicol and erythromycin was grown in considerable quantities from the blood-culture An identical organism was isolated from the patient's throat, the ileostomy, a bedsore, and a subsequent metastatic abscess over the sternum Erythromycin 1 5 g daily was given for three weeks and chloramphenicol 1 g daily for ten days, the blood-culture was sterile at the end of the first week

Case 4—A woman, aged 40, so ill with ulcerative colitis that operation was impossible on admission, had been receiving cortisone for nine months An abscess due to disintegration of the sigmoid colon was present in the left iliac fossa Attempts to prepare her for colectomy proved fruitless She became dyspnœic with signs of pericarditis, at which time *Staph albus* was grown from blood-culture She died two days later from a pulmonary embolus

Case 5—A woman, aged 40, collapsed eighteen hours after primary colectomy undertaken on account of severe ulcerative colitis previously treated with hydrocortisone enemas In the absence of an obvious cause for the collapse, and since the



Data on case 1 Cortisone was withdrawn on the eighth postoperative day and corticotrophin on the twelfth postoperative day

patient appeared to be dying, intravenous hydrocortisone was given with an immediate satisfactory response Chloramphenicol was added as protection against possible infection during steroid therapy, nevertheless the patient had a rigor and her temperature rose to 101 5°F three days later *Escherichia coli* was grown from the blood, though therapy with chloramphenicol was intensified, subsequently an enterococcus was grown in addition to the coliform organisms, so neomycin had to be given in addition After many vicissitudes due to bleeding and coagulation defects the patient died on the eighth postoperative day in hepatic coma The organisms were isolated from hepatic blood samples taken immediately after death

Case 6 —The situation with a man, aged 24, differed from that in the foregoing cases since staphylococcal septicæmia developed two months after cessation of cortisone therapy (100 mg daily for two months) for ulcerative colitis and two to three weeks after operation for this condition without steroid cover *Staph pyogenes*, resistant only to penicillin, was grown from blood-culture, the condition was controlled by tetracycline

The association of corticosteroids and septicæmia may only have been coincidental in this case

2 cases of septicæmia, 1 fatal, have also been seen in patients who had never received cortisone

Case 7 —A paraplegic man, aged 42, had a plastic repair of a decubitus ulcer over the right ischium He was discharged from hospital with the wound healed except for a linear area at one edge of the skin-flap A week later he was readmitted in a confused and toxic state and, though afebrile, the gluteal area was inflamed with pus discharging from the linear area mentioned previously, penicillin and streptomycin were given Four days later the patient's general condition was poor with temperature of 103°F and pulse-rate 130, a blood-culture was taken and the whole flap laid open Proteus sensitive to streptomycin and chloramphenicol but insensitive to tetracycline, and *Staph pyogenes* insensitive to all antibiotics except chloramphenicol and erythromycin, were found to be growing from the swab taken on admission Combined therapy with chloramphenicol (1 g daily) and erythromycin (1 6 g daily) was therefore begun, twenty-four hours later the resistant staphylococcus was isolated from blood-culture These drugs were continued for a further two weeks, at the end of which all blood-cultures were sterile

Case 8 —A man, aged 49, was treated by circumcision for severe phimosis and extensive balanitis which had caused meatal stenosis He was provided with a meatal dilator and instructed in its use Three months later the patient was readmitted with a five-day history of dysuria, extreme frequency, and rigors, penicillin 1 mega unit b d had been administered by his private practitioner without effect On admission he was toxic (temperature 105°F, pulse-rate 130) Acute cystitis and prostatitis complicated by ascending pyelonephritis was diagnosed, streptomycin 1 g b d was given The following morning his clinical condition was better, his temperature had fallen to 100°F and pulse to 110 That evening, however, his temperature rose to 104°F and pulse-rate to 140, and an erysipeloid rash appeared on the left forearm and later elsewhere Urine culture revealed proteus and *Staph pyogenes* resistant to all antibiotics except chloramphenicol and erythromycin, so treatment with chloramphenicol was started immediately (1 25 g daily) The following day the patient was disorientated with a temperature of 104°F, in addition to the chloramphenicol, erythromycin was given by continuous drip (2 4 g per day) The blood-culture yielded a growth of *Staph pyogenes* insensitive to all antibiotics except chloramphenicol and erythromycin Nevertheless the patient's condition became worse and he died seventy hours after admission At necropsy acute suppurative prostatitis with thrombosis in the periprostatic plexus was found, basal hæmorrhagic cystitis was also present, but there was no evidence of pyelonephritis

Discussion

These cases are reported to draw attention to the new era of infection that has arisen causing septicæmia to

CAUSAL ORGANISM IN EIGHT CASES OF SEPTICÆMIA

Case no	Age (yr)	Sex	Diagnosis	Corticoids administered	Organism	Sensitivities: Penicillin	Streptomycin	Chloramphenicol	Tetracycline	Erythromycin	Neomycin	Result
1	44	M	Ulcerative colitis	Yes	*Staph pyogenes*	−	−	+	−	+		Recovered
2	40	M	Ulcerative colitis	Yes	*Cl welchii* *Diplococcus mucosus*	+ −	− −	− −	− +	N K +		Recovered
3	33	M	Crohn s colitis	Yes	*Staph pyogenes*	−	−	−	−	+		Recovered
4	40	F	Ulcerative colitis	Yes	*Staph albus*	−	−	−	−	−		Died
5	40	F	Ulcerative colitis	Yes	Coliform Enterococcus	N K N K	± −	− −	− −	N K N K	+	Died
6	24	M	Ulcerative colitis	Yes, but therapy ceased before positive blood-culture	*Staph pyogenes*	−	−	−	+	−		Recovered
7	42	M	Decubitus ulcer	No	*Staph pyogenes*	−	−	+	−	+		Recovered
8	49	M	Suppurative prostatitis	No	*Staph. pyogenes*	−	−	−	−	−		Died

+ = sensitive. − = insensitive N K. = not known become commonplace, and to the two principal factors conspiring to produce it The emergence of the virulent resistant staphylococcus has been well documented (Shooter et al 1957, McDonald and Timbury 1957) Its dangers are clearly demonstrated by case 8, a man who entered hospital for a trivial operation, only to acquire the hospital staphylococcus, which, though sensitive to chloramphenicol and erythromycin in vitro, responded in no way to these drugs in vivo so that he died of fulminating septicæmia

Less well recognised is the effect of corticosteroids, indeed this has even been discounted (Popert and Davis 1958) But there is ample clinical and experimental evidence to incriminate these drugs

Shaper and Dyson (1955) reported 2 deaths due to staphylococcal septicæmia in patients receiving cortisone, one for rheumatoid arthritis and the other for exfoliative dermatitis, and Dubois-Ferrière (1951) reported another such case Hayes and Kushlan (1956) recorded 2 cases of " bacteræmia " due to resistant strains of staphylococci in 12 patients receiving steroids for ulcerative colitis, 1 patient died, the other developed multiple metastatic abscesses but eventually recovered Smith and Cleve (1957) record a further death from staphylococcal septicæmia in a patient receiving cortisone

Thomas (1955) showed that an injection of streptococci intradermally into rabbits causes a brisk local reaction followed by prompt healing If cortisone is given before the injection of streptococci there is no local response and the rabbits appear healthy for a few days then die suddenly, at necropsy colonies of streptococci are found in all tissues, there being practically no inflammatory response, the animal thus appears to become a living culture-medium in the interval between injection and death

This state of affairs was closely paralleled in several of our patients—notably case 2, who felt perfectly well despite the profuse growth of *Cl welchii* in his peripheral blood The danger period is usually at the end of the first postoperative week As might be expected from the behaviour of infections in Cushing's syndrome many of the overt signs of septicæmia are often absent, and a blood-culture should be performed in any patient receiving corticosteroids who has pyrexia or tachycardia without obvious cause, chloramphenicol cover should be considered for any patient undergoing surgery for an infective condition while under steroid therapy, leaving erythromycin in reserve for further developments

Septicæmia associated with corticosteroids is modified in its clinical manifestations, it appears also to differ from unattenuated septicæmia in its better response to therapy Of 6 patients in the cortisone group 2 died, but these deaths were as much from other causes (liver failure, &c) as from septicæmia and probably would have occurred even without infection Provided the condition is recognised, even resistant staphylococcal infections during corticosteroid therapy may be brought under control this has proved more difficult in the group not receiving corticosteroid therapy

Summary

8 cases of septicæmia have been seen in a ten-month period

In 5 and possibly 6 patients corticosteroid therapy appeared to have played a part in precipitating septicæmia with modified clinical manifestations

In 6 patients the organism was *Staph pyogenes*, which was resistant to penicillin in most cases and to all antibiotics in 1 case

Before corticosteroid therapy is instituted possible complications, notably septicæmia, should be carefully considered

We wish to thank Dr E Bulmer and Mr V Brookes for permission to report case 6, and Mr O T Mansfield for case 7

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HYPERPYRUVATURIA FOLLOWING INTRAVENOUS ADMINISTRATION OF FRUCTOSE

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The wish to provide, in certain diseases, the sugar which the patient can most easily assimilate has stimulated much work on the metabolic differences between glucose and fructose This work indicates that fructose is more assimilable than glucose and is better metabolised in diabetic patients and in experimental diabetes (Pletscher 1953, Smith 1953, Renold and Thorn 1955, Leuthardt 1956, Hoenig 1957)

Most papers on this subject refer to the liver, which metabolises 30–50% of intravenously infused fructose (Mendeloff and Weichselbaum 1953) We deal here with some aspects of kidney function under the influence of glucose and fructose Our results show that, on intravenous administration fructose increases the urinary excretion of pyruvate, mainly through changes of renal tubular activity Glucose does not do this

Investigation and Results

The patients studied were selected from the wards of the hospital All had a carbohydrate intake exceeding 200 g daily and fasted for more than twelve hours before the test

25 g of glucose or fructose, as a 40% solution, was injected over a period of three to five minutes Samples of venous blood for plasma-pyruvate estimation were withdrawn homolaterally through an indwelling needle before the injection of the sugar (two samples) and then, after the injection, at fifteen-minute intervals for sixty minutes Before the injection one urine specimen was collected for at least one hour After the sugar was given a second urine specimen was again collected for at least one hour At the beginning of the experiment 500 ml of clear tea without sugar was administered

The urinary and plasma pyruvate content were determined by the method of Friedemann and Haugen (1943) as adapted by Slavik and Michalec [*] (1949) The quantity of urinary pyruvate was calculated from the product of the urine volume and the urinary concentration of pyruvate The quantity of pyruvate filtered was estimated as the product of the average glomerular filtration-rate (estimated as the endogenous-creatinine clearance) × the average plasma-pyruvate level Plasma and urine creatinine were estimated by the method of Bonsnes and Taussky (1945), it was not influenced by the pyruvate actually present From the quantity filtered and excreted, the percentage of pyruvate reabsorbed was calculated

Two series of investigations were performed In the first, urinary pyruvate excretion was studied in control patients with miscellaneous non-metabolic disorders (25

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[*] Sodium pyruvate for the calibration curve was kindly supplied by F Hoffmann, LaRoche & Co, Basle

TABLE I—EFFECT OF FRUCTOSE (40% SOLUTION INJECTED INTRAVENOUSLY) ON THE RENAL EXCRETION, FILTRATION, AND REABSORPTION OF PYRUVATE A—FASTING VALUES, B—VALUES FOLLOWING THE INJECTION, C—DIFFERENCE

Subject no	Pyruvate excreted (μg min. 1 73 m²)			Pyruvate filtered (μg min /1 73 m²)			Pyruvate reabsorbed (% of pyruvate filtered)		
	A	B	C	A	B	C	A	B	C
1	23	92	69	2000	1780	−220	99	95	−
2	24	183	159	2360	2180	−180	99	92	−
3	20	92	72	2420	2500	80	99 5	96 5	−
4	12	106	94	1710	1820	110	99	94	−
5	16	209	193	1850	2350	500	99	91	−
6	34	169	135	1170	1720	550	97	90	−
7	15	184	169	1380	2130	750	99	91 5	−
8	13	196	183	1340	2040	700	99	90	−
9	10	106	96	1010	1740	730	99	94	−
10	14	122	108	1220	2180	960	99	94 5	−
Average	18 1	145·9	127 8	1646	2044	398	98 9	92 9	−
P		<0 001			0 01–0·02				<0

investigations in 7 patients with both glucose and fructose loading on alternate days, 10 patients with fructose, and 1 patient with glucose alone) and in cirrhotic patients 23 investigations in 8 patients with glucose and fructose, 5 patients with fructose, and 2 patients with glucose alone In the second, renal studies were performed in addition in 10 arbitrarily selected subjects

Injection of fructose produced, both in the control and cirrhotic groups, a pronounced increase in urinary pyruvate (table, figs 1–3) The average values (expressed in μg per min per 1 73 sq metre of body-surface) were 117 9 μg (range 45 4 to 206 6) in the first, and 116 5 μg (35 3 to 222 9) in the second group (P<0 001) The increase following glucose was insignificant 3 3 μg (−4 2 to 12 6) and 2 9 μg (− 6 4 to 27 5) (0 10 <P<0 20, 0 30<P<0 40)

The average increase in pyruvate filtered following fructose was 398 μg per minute per 1 73 sq m (−220 to 960) The average decrease in pyruvate reabsorbed was 6% (range 3–9%) of the quantity filtered

Discussion

In a previous paper (Hoenig 1957) we showed that intravenous administration of fructose brings about a greater increase in urinary inorganic phosphorus than administration of glucose Our present results show that the same is even more true of the excretion of pyruvate We have found only two reports on this subject in one (Sasaki 1950) a *decreased* pyruvaturia was found, and in the other the *concentration* of urinary pyruvate increased after administration of fructose (Enoki and Mukaiama 1952)

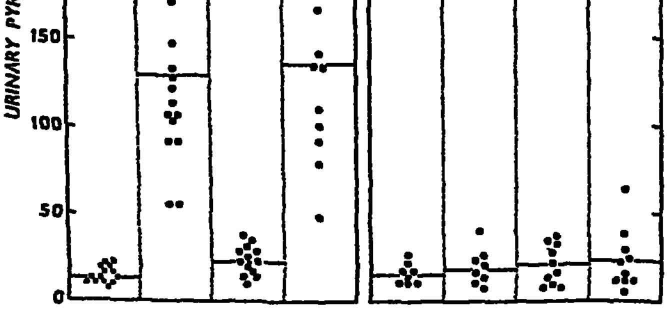

Fig 1—Values of urinary pyruvate (μg per minute per 1 73 sq metre) before and after intravenous administration of fructose and glucose The rise after fructose is striking There is only an insignificant rise following glucose The control and the cirrhotic groups do not differ

The increased excretion of pyruvate diminished rapidly In 3 of 7 patients only moderate hyperpyruvaturia was present during the second hour after the injection of fructose

From the therapeutic standpoint we were interested in whether this hyperpyruvaturia depended on the duration of the infusion period 500 ml of 10% fructose solution was infused during 80–110 minutes in 3 subjects The hyperpyruvaturia was less evident than after rapid administration The increase in urinary pyruvate during the infusion was 85 2, 69 4, and 95 7 μg per minute per 1 73 sq metres

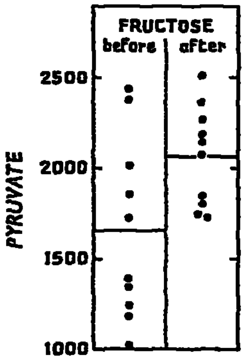

Fig 2.

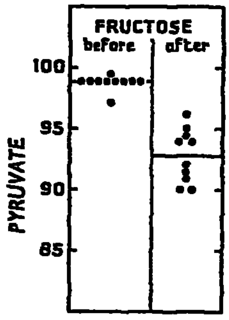

Fig 3

Fig 2—Values of filtered pyruvate (μg per min per 1 73 sq m) before and after intravenous administration of fructose

Fig 3—Values of pyruvate reabsorbed before and after intravenous administration of fructose (of the filtration values) The drop in the reabsorption-rate is the main cause of the hyperpyruvaturia.

To explain the observed hyperpyruvaturia, it would be necessary to know the mechanism of renal excretion of pyruvate We have so far not found any reports on this Since other related acids (e g , lactic acid) are eliminated by filtration and reabsorption (Miller and Miller 1949), we can assume that the same mechanism is involved in the renal excretion of pyruvate

The hyperpyruvaturia following fructose administration is therefore attributable either to the increase in the quantity of pyruvate filtered or to depression of its tubular reabsorption

Our results suggest that the observed phenomenon reflects a depressed renal tubular reabsorption of pyruvate rather than alterations in the filtration mechanism the average increase in pyruvate filtered could not by itself produce the hyperpyruvaturia observed, and there was hyperpyruvaturia in cases where the pyruvate filtered decreased (cases 1 and 2, table I)

The mechanism of this depression is obscure There may be either a competition between fructose and pyruvate for a substance implicated in their tubular reabsorptive mechanism, or the reabsorption of pyruvate may be inhibited by an intracellular metabolic product The observation that fructose and pyruvate inhibit each other's uptake by the perfused liver (Laguna et al 1956) may be of some interest in this connection

Cirrhotic patients behaved similarly to control subjects In some patients we found a higher fasting value of urinary pyruvate This has been reported elsewhere in severe liver failure (Amatuzio and Nesbitt 1950, Thompson 1956) According to our results, it is due to a depression of the tubular reabsorption of pyruvate

In conclusion, we can say that intravenous administration of fructose interferes with the metabolism of the renal tubules This leads to an increase in the excretion of pyruvate, inorganic phosphate (Hoenig et al 1958), and perhaps of other metabolites Further studies are required, to assess the clinical importance of these observations

Summary

Infused intravenously, fructose increases the renal excretion of pyruvate Glucose does not do this

The increased renal excretion is mainly due to depression of the tubular reabosorption of pyruvate

In most cases it ceases within an hour of the administration of the sugar

Its extent depends on the infusion-rate

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SUCCESSFUL PREGNANCY UNDER TREATMENT FOR MALIGNANT HYPERTENSION

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So far as we are aware, no report has yet appeared of a successful pregnancy in a patient in whom malignant hypertension has been controlled with hypotensive drugs We report a patient with a fourteen-year history of severe hypertension who gave birth to a surviving premature infant after two previous episodes of malignant hypertension, one four years and the other fourteen years ago

Case-report

In February, 1942, at the antenatal clinic at University College Hospital, a woman aged 22 was found to be hypertensive in the twentieth week of her first pregnancy, her blood-pressure being 220/140 mm Hg Malignant hypertension was diagnosed because of bilateral papillœdema and retinitis Abdominal hysterotomy was done at twenty-six weeks In September, 1942, she was admitted to the London Hospital for investigation of the hypertension Immediately before admission she had had frequency of micturition, dysuria, and lumbar pain Her blood-pressure varied between 190/130 and 215/140 mm Hg, but she showed no other abnormality, and the papillœdema and retinitis noted in February had completely regressed Renal function was normal, apart from persistent albuminuria A culture of urine yielded a scanty growth of *Staphylococcus albus* and a moderate growth of coliform bacilli

In 1945 the patient consulted the gynæcological department at the Westminster Hospital, being anxious to undertake a further pregnancy Her blood-pressure was 210/140 mm Hg, her blood-urea level 40 mg per 100 ml, and an intravenous pyelogram normal, but her urine contained protein 100 mg per 100 ml In September, 1946, when she miscarried a macerated fœtus at 26 weeks, her blood-pressure was 230/180 mm Hg

In 1951, at the age of 31, she attended the gynæcological department at Hammersmith Hospital Her blood-pressure was 210/140 mm Hg, and her optic fundi showed arterial narrowing but no retinitis Her urine was now, for the first time, free from albumin, her blood-urea level was 21 mg per 100 ml, and the specific gravity of her urine ranged from 1 002 to 1 020

She next presented at the ophthalmic clinic of the Hospital in December, 1952, complaining of blurring of vision for a month Bilateral papillœdema with hæmorrhages and exudates was noted, and she was admitted to a medical ward An additional relevant fact in her history was the absence of any hypertensive disease in her family In addition to the visual difficulties she had had breathlessness on exertion and ankle swelling for two weeks and two attacks of paroxysmal nocturnal dyspnœa She was dyspnœic, her pulse-rate was 120 and blood-pressure 230/160 mm Hg A presystolic triple rhythm was noted, and she was in congestive heart-failure, soon after admission she had an attack of acute pulmonary œdema Radiography of her chest showed considerable left ventricular hypertrophy, which was confirmed by electrocardiography An unusual feature was a prolongation of the P–R interval (0 24 sec), which has been present intermittently on subsequent records A transient albuminuria was present while the patient was in heart-failure Her blood-urea level was 21 mg per 100 ml, and isosthenuria was present She improved rapidly on treatment with subcutaneous hexamethonium bromide together with digoxin, diuretics, and a low-salt diet She was stabilised on subcutaneous hexamethonium bromide 60 mg thrice daily, which reduced the blood-pressure to 110/70 mm Hg in the erect position an hour after the injection On this treatment papillœdema resolved completely in two months

A year later the patient's treatment was changed to subcutaneous pentolinium 60 mg thrice daily with a satisfactory hypotensive response

In 1955 reserpine ('Serpasil') 0 1 mg three times a day was added to the treatment, and during follow-up from December, 1952, to June, 1956, the patient remained subjectively extremely well Radiological and electrocardiographic evidence of left ventricular hypertrophy persisted

Successful Pregnancy

In June, 1956, at the age of 37, the patient was found to be six-weeks pregnant As she was most anxious to continue with the pregnancy, and as her blood-pressure was easily controlled, it was decided that she should continue under close supervision She was given a high-protein low-carbohydrate low-salt diet, and strict attention was paid to her weight She was seen at weekly intervals, and much variation was noted in her response to hypotensive drugs, together with a definite decrease in dosage requirements The total daily pentolinium dosage was decreased from 180 to 120 mg, but even with this reduction readings of 95/60 mm Hg were noted an hour after the injection In view of possible impairment of the placental circulation she was admitted at the fifteenth week of pregnancy She was transferred to oral mecamylamine 10 mg b d together with the previous dosage of reserpine She continued her weekly attendances at the antenatal clinic Her weight which at the beginning of pregnancy was 151 lb , remained almost stationary She was last seen at this clinic when twenty-nine weeks pregnant. Her blood-pressure in the erect position was 170/120 mm Hg, and in the recumbent 200/140 mm Hg She had no œdema, and her weight showed a sudden drop of 2 lb 4 oz from that of the previous week She felt perfectly well but was admitted for observation

Two days later she had a sudden onset of colicky lower abdominal pain and a vaginal hæmorrhage of about 300 ml The fœtal heart was still heard She went spontaneously into labour eight hours later and gave birth spontaneously to a healthy male infant weighing 4 lb 1 oz The placenta followed rapidly with about 200 ml of blood-clot, it weighed 1 lb 2 oz and had obviously been involved in an accidental hæmorrhage The patient's blood-pressure after delivery was 170/125 mm Hg in the supine position Over the next month a gradual increase in mecamylamine dosage to the present daily total of 45 mg was necessary The baby was discharged when at the age of 36 days, weighing 5 lb 10 oz and has remained fit and well

Discussion

The pregnancy produced a live baby in spite of two previous episodes of malignant hypertension The first of these occurred during pregnancy in 1942 and reverted to benign hypertension, judged by retinal changes, after termination of the pregnancy Malignant hypertension was again diagnosed in 1952 and responded to hypotensive drugs, on which the patient has been maintained until now

The original hypertensive episode in 1942 must be regarded as " chronic hypertension " and not as a pregnancy toxæmia, because of severe hypertension at the twentieth week of pregnancy Albuminuria persisted for at least seven months after termination of the pregnancy This albuminuria is of considerable interest because the urine at present is free from albumin, as it has been on numerous examinations in the past fifteen years Albuminuria is almost universal in malignant hypertension (Ellis 1938, Kincaid-Smith et al 1958), and its absence here probably indicates that the vascular changes of malignant nephrosclerosis had not yet developed when hypotensive therapy was instituted in 1952 The subsequent favourable course and normal renal function support this hypothesis

The ætiology of the hypertension in the present case is by no means clear The rarity of essential malignant hypertension in this age-group (Platt 1948, Kincaid-Smith et al. 1958) caused us to seek some renal or other cause The dysuria and positive urine culture in 1942 introduced the possibility of chronic pyelonephritis as a causal factor This condition is notoriously difficult to diagnose, but, in the absence of any further positive evidence, and with repeated normal intravenous pyelograms and urine deposits, we think it unlikely Investigation has provided no other evidence of any underlying cause of the hypertension Pregnancy was clearly the precipitating factor in 1942

Irrespective of the cause of malignant hypertension this condition carries a very poor prognosis, most patients dying in three months Survival beyond two years is exceptional in untreated cases (Kincaid-Smith et al 1958) A slight fall in the blood-pressure after the abdominal hysterotomy in 1942 was associated with disappearance of the papillœdema and retinal exudates in seven months

The second episode of malignant hypertension, in 1952, responded readily to hypotensive drugs Few data are available for the prognosis of malignant hypertension in pregnancy, but death from uræmia may certainly occur within a short period in spite of termination of the pregnancy (Heptinstall 1953, Currens et al 1956, Kincaid-Smith et al 1958)

Termination of this pregnancy was at first contemplated in view of the past history and the well-known risks to the mother Because of the patient's insistence, however, it was decided to continue the pregnancy under close supervision

Young (1952) showed that hexamethonium bromide accumulates in the amniotic fluid of animals Morris (1953) reported deaths from paralytic ileus in two of ten infants where hexamethonium bromide had been used as a hypotensive agent during pregnancy, he consequently advised that hexamethonium should be withheld at least twenty-four hours before delivery Because of its diffusibility we expected mecamylamine to produce similar effects in the fœtus and had therefore intended to discontinue it a week before cæsarean section at thirty-four weeks Spontaneous premature labour prevented these precautions, but in spite of full doses of mecamylamine until the time of delivery and the excretion by the infant of 0 53 mg of mecamylamine, no paralytic ileus or other complications developed

Although commonly the child in cases of hypertension is smaller than usual for the period of gestation, in this case, with an undoubted gestation period of twenty-nine weeks and two days, the infant was unusually large, suggesting that hypotensive treatment had influenced favourably the placental ischæmia known to be associated with maternal hypertension (Browne and Veall 1953)

The decreased pentolinium requirements between the eleventh and fourteenth weeks of the pregnancy interested us because of the known physiological fall in the blood-pressure which takes place in the second trimester (Browne and Browne 1955)

In view of the success reported here, there may be reason to give hypotensive drugs such as mecamylamine a more extensive trial in similar cases An integral part of the management should be the maintenance of the erect posture as much as possible instead of the traditional rest in bed

Summary

A successful pregnancy ensued in a patient in whom malignant hypertension was controlled with hypotensive drugs Hypotensive drugs, particularly mecamylamine, should be given a more extensive trial in severe hypertension in pregnancy

We are grateful to Prof J McMichael, under whose care this patient was treated from 1952 until 1956, Dr J P M Tizard, who supervised the management of the premature infant, Dr Donald Hunter and the departments of obstetrics and gynæcology at the Westminster and University College Hospitals for details about the patient s previous hospital admissions, and Dr M D Milne for estimating the mecamylamine excreted by the premature infant

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"KWASHIORKOR" IN AN ADULT
DUE TO AN INTESTINAL BLIND LOOP

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WHENEVER uncontrollable diarrhœa follows an abdominal operation short-circuiting of the small bowel should be suspected, according to Alvarez (1957) The patient now reported had signs of severe malabsorption after a side-to-side anastomosis had been made in the lower ileum His hair turned red while the malabsorption was at its worst, and reverted to its normal brown colour once he was cured by restoration of intestinal continuity

Case-report

A white man, born in 1916, underwent subtotal gastrectomy (Polya-Hofmeister) for a bleeding chronic duodenal ulcer in 1950 He was readmitted to hospital in July, 1953, with acute intestinal obstruction At laparotomy a coil of small bowel was found to be kinked and adherent to the anterior abdominal wall at the site of the gastrectomy incision The adhesions were separated and the torn serosal surfaces covered with peritoneum Obstruction recurred on the seventh postoperative day Laparotomy showed part of the ileum to be twisted, swollen, and œdematous, but still viable, two small perforations were closed, and the loop was excluded by means of a side-to-side anastomosis

Onset of Symptoms

After this operation his stools were perceptibly looser than they had previously been, but he remained well till May, 1955, when he first noted cramps in the legs His physician prescribed injections of vitamin B_{12} in February, 1956, and these gave him fair relief Towards the end of 1955 his appetite and food-intake increased greatly, but he lost 63 lb in the eight months before admission

During April, 1956, his health sharply deteriorated He passed 6–15 pale, offensive, porridgy stools a day, his abdomen became distended, and he felt very weak and listless His hair, normally brown, became red and stopped growing (he needed only one haircut in four months and rarely shaved) Body-hair fell out, leaving scanty red axillary and pubic hair The nails of the fingers and toes ceased growing His voice became hoarse, and libido was lost

Investigations

Studies elsewhere at this time showed that the hæmoglobin was 8 8 g per 100 ml and that there was macrocytosis and poikilocytosis The bone-marrow showed normoblastic erythropoiesis The serum-albumin was 1 2 g and the serum-globulin 1 8 g per 100 ml In August, 1956, during an attack of tetany, the serum-calcium was 7 0 mg and the inorganic phosphorus 3 8 mg per 100 ml A well-functioning subtotal gastrectomy was seen on barium-meal examination, the barium enema was negative

Treatment

Treatment with penicillin, streptomycin, tetracycline, and neomycin, and with prednisone, did not improve his condition At laparotomy on Sept 3, a gastrocolic fistula was sought but not found His condition was poor, and a more thorough search was not made

Two weeks later he was admitted to the Groote Schuur Hospital He was very wasted, with a receding hair-line, dry reddish hair, and mild pellagrous skin changes His tongue was bald and red, and he had cheilosis and angular stomatitis There was no peripheral œdema The cardiovascular and respiratory systems were normal, the blood-pressure was 110/80 mm Hg The abdomen was distended and bowel sounds were increased The prostate gland was barely palpable and the testes were retracted and small The legs were weak and tender on deep pressure, with decreased perception of pin-prick and absent ankle reflexes

The urine was normal The hæmoglobin was 10 5 g per 100 ml, and the blood smear appeared normal The serum-albumin was 3 1 g per 100 ml and serum-globulin 3 0 g, serum-cholesterol 98 mg per 100 ml, and serum-alkaline phosphatase 7 1 Bodansky-Shinowara units The blood-urea, serum-bilirubin, serum-electrolytes, and oral-glucose tolerance curve were within normal limits Plain radiographs of the chest, abdomen, and vertebral column were normal Barium-meal and barium-enema studies were again negative

The electrocardiogram showed sharp T-wave inversion in leads V_1 to V_3, which improved within a week of the start of therapy The basal metabolic rate was –10% The stools were grossly fatty and contained no occult blood

Discharge and Readmission

In view of the recent negative laparotomy, a blind loop was not seriously considered Moderate improvement resulted from a low-fat, low-residue diet with vitamin B_{12}, folic acid, and multivitamin supplements, and he was discharged a month after admission A relapse led to his readmission on Nov 24, 1956 His legs were very painful, and evidence of peripheral neuritis had increased His vision was poor, especially at night, and he was found to have pallor of the temporal halves of the optic discs Photophobia was troublesome The legs were moderately œdematous The serum-albumin had fallen to 1 9 g per 100 ml and the serum-globulin was 2 3 g A three-day fat balance (intake 70 g a day) showed 62% absorption Needle biopsy of the liver showed significant liver-cell damage in a regenerative phase (Dr C J Uys)

Preparation and Operation

As the patient's condition had deteriorated, and a blind loop appeared to be the likeliest cause of the malabsorption, it was decided to search for it again In preparation the patient was given a high-calorie diet, transfusions of blood and serum, and vitamin supplements He was ravenous, on an average day the diet kitchen dispensed meals containing 528 g of protein, 483 g of fat, and 895 g of carbohydrate, providing him with about 10,000 calories In addition he ate whatever residue was available from the ward supplies His vision improved, the skin lesions disappeared, the œdema decreased, and he gained a little weight, but his legs remained painful and weak The serum-albumin rose to 4 2 g per 100 ml

At laparotomy (Dr D J du Plessis) a short-circuited loop six feet in length was found, three feet from the ileocæcal valve This was unpicked and normal continuity restored His postoperative recovery was dramatic His appetite became normal, the stools were well-coloured, formed, and less frequent, and he gained 35 lb in the twenty-one days after operation His hair became thick and dark brown, and after two weeks he had to shave every day Axillary, pubic, and body hair also became profuse and darker, and his nails started to grow normally His tongue was no longer red and smooth Libido returned a month after the operation, after two months his prostate felt normal, the testes were normal in size and no longer retracted Vision returned to normal, but pallor of the temporal halves of the discs has persisted

Two months after the operation the electrocardiogram was completely normal, the serum-cholesterol was 273 mg per 100 ml, the serum-albumin was 5 3 g per 100 ml, and the serum-globulin 2 8 g A fat-balance study showed 94% absorption His sole remaining disabilities were due to the peripheral neuritis and were improving with physiotherapy

Discussion

IT has only recently been realised that the construction of blind loops of small intestine can produce steatorrhœa and megaloblastic anæmia "Pernicious anæmia" due to a surgical fistula (between jejunum and ascending colon) was first reported by Little et al (1929) Cameron et al (1949a) reviewed 23 cases of macrocytic anæmia due to intestinal anastomoses and 37 due to strictures of the small bowel, Halsted et al (1956) brought the total for both types to 76

Cameron et al (1949b) showed in rats that construction of an intestinal loop that could fill with normal peristalsis, but not empty itself, produced macrocytic anæmia This was true only of loops in the upper small bowel, yet in our case the site was in the lower ileum, and in others the communication has been between lower ileum and colon (Halsted et al. 1956)

It is believed that stagnation in such a loop leads to bacterial infection which spreads into and irritates the rest of the small intestine (Witts 1956) Sammons et al (1956) have discovered a strain of *Streptococcus fæcalis* able to synthesise fats in vitro, such organisms thriving in a cul-de-sac may be able to divert vitamin B_{12}, folic acid, and other substances from the host Presumably absorption is decreased from those areas of bowel irritated by the overflowing exudates, but Jackson and Linder (1951) believe that an additional "toxic" factor is necessary to produce a sprue-like syndrome Stagnation is likewise thought to cause the malabsorption found in patients with jejunal diverticulosis (Badenoch et al 1955) and intestinal strictures (Gardner 1957) In both the blind-loop syndrome (Halsted et al 1956) and jejunal diverticulosis (Evans 1956), oral aureomycin has improved the absorption of ^{60}Co-labelled vitamin B_{12} from the gut, presumably by killing organisms that had been taking it up Our patient had not responded clinically to antibiotic therapy (including a course of tetracycline)

An abnormal intestinal pattern is found on barium-meal examination in most cases of enterogenous steatorrhœa, but tends to be absent in the blind-loop syndrome (Gardner 1957), as it was in this case Two years' delay between the operation and the development of anæmia is recognised (Halsted et al 1956) In our case erythropoiesis was normoblastic at the time of bone-marrow examination, but he had received vitamin B_{12}

Our patient could obviously make very little use of his colossal food intake. The appetite is often retained in steatorrhœa (Ingelfinger 1957), but such an increase is very unusual.

Many of the other features are uncommon or unknown in the malabsorption syndrome or in simple starvation We can find no reference to such hair changes in steatorrhœa In prisoners-of-war in Japanese hands (Smith and Woodruff 1951) and in experimental human starvation (Keys et al 1950), hair was lost from the scalp, but neither reddening nor changes in the body-hair were reported In a case of massive intestinal resection where signs of severe malnutrition developed the patient's body-hair regrew after the operation and he shaved daily (Jackson et al 1951) The colour changes in the hair in our case seem analogous to those in kwashiorkor in infants with protein malnutrition (Brock and Autret 1952) Severe hypoproteinæmia is occasionally reported in idiopathic steatorrhœa (Adlersberg et al. 1957, Forshaw 1957), and is common when malabsorption is due to a bowel short-circuit (Cooke 1952)

The visual disturbance was thought to be due to retrobulbar neuropathy Smith and Woodruff (1951) suggested that "deficiency amblyopia" was not due to beriberi or pellagra, the therapeutic response to vitamin A, aneurine and nicotinamide was poor, but their patients did well on riboflavine-containing foods Irreversible optic atrophy might develop in not less than six months

The peripheral neuritis in our case was probably associated with aneurine deficiency, but pain in the feet and legs was unduly prominent and did not respond as well to therapy Smith and Woodruff (1951) thought that this "burning-feet syndrome" was different from the polyneuritis of beriberi, and found that it did not improve on treatment with aneurine. The serial electrocardiographic changes are those often seen in "beriberi heart-disease" in Cape Town (Schrire and Gant, 1955) A return to complete normality is the rule, and the electrocardiographic changes may be the only manifestations of the cardiac involvement

In Jackson et al.'s case (1951) libido was lost and erections stopped, but secondary sex characteristics were retained, at necropsy there was practically no spermatogenesis (Linder et al 1953) In our patient the prostate gland and testes were small, they returned to normal once the loop had been unpicked In rats, Addis et al (1936) showed that starvation for seven days caused the loss of 29% of the protein content of the prostate, compared with 40% from the liver and none from the testes, perhaps the changes are similar in man Stefko (1928) found that atrophy of the seminiferous tubules was rare in starved adults and thought that the testis resisted starvation better than the ovary Unfortunately 17-ketosteroid assays and testicular biopsies were not done in our patient.

Summary

A case is presented of iatrogenic steatorrhœa, due to a surgically-constructed blind loop in the ileum Two years after this operation extremely severe signs of malabsorption developed, with hypoproteinæmia, reddening of the hair, retrobulbar neuropathy, peripheral neuritis, and sexual changes Operative correction of the abnormality of the bowel led to rapid and almost complete resolution of the secondary defects

We are grateful to Dr L. Mirvish and Dr R L. Tobias for their interest and advice, and we thank them and Dr N H G Cloete, medical superintendent, Groote Schuur Hospital, for permission to study and publish this case. This study was aided by a grant from the Cape Town city council

ADDENDUM

Temporary redness of the hair has been described by S M Mellinkoff (*Amer J digest Dis* 1957, 2, 738) in a case of ulcerative colitis the patient's hair turned red with malnutrition and returned to its normal brown colour when his general condition improved Peripheral œdema and hypoproteinæmia (serum-albumin 2 5 g per 100 ml) were present

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Preliminary Communication

POLIOVIRUS TYPE 1 ISOLATED FROM A BUDGERIGAR

ALTHOUGH numerous animals, including dogs, cats, and even moles,[1] have been named as possible reservoirs of poliomyelitis virus, confirmatory evidence from the laboratory has always been lacking Possible avian reservoirs were suggested when a time relationship was observed between outbreaks of fowl paralysis and the human poliomyelitis epidemic in South Africa in 1948,[2] but no association was proved

We describe here an incident in which there seems little reason to doubt that a budgerigar became infected with poliovirus type 1 and excreted this virus for at least three weeks The main purpose of this preliminary communication is to draw attention once more to the possibility of transmission of poliomyelitis by domestic pets

The budgerigar in question came into contact with a boy aged 9 on Aug 15, 1957, at which time the bird was recovering from paralysis of its legs This bird was allowed out of its cage, and once took hold of the boy's lip with its beak and held on to him until it was removed by the boy's mother Another bird which had been kept in the same cage had died from a similar attack of paralysis a few days earlier The child became ill on Aug 22, developed signs of bulbar poliomyelitis on Aug 24, and died four days later Type-1 poliovirus was recovered from his stool

The possibility of an association between the illnesses of the birds and the boy first prompted examination of droppings from the bird about mid-September Culture of this material in HeLa cells yielded poliovirus type 1 The possibility of accidental laboratory contamination was excluded when the same virus was isolated from the same specimen of droppings by a different worker in a different laboratory

On Oct 7 a second sample of droppings examined in HeLa cells yielded poliovirus type 1 On the same day the budgerigar was killed and the intestinal contents, collected at necropsy, were examined in HeLa cells Poliovirus type 1 was again isolated In each instance the cytopathogenic effects of the virus were observed in the first passage Unfortunately it was not possible to obtain serum from the bird for antibody assay

The viruses were identified by neutralisation tests in HeLa cells using high-titre antiserum prepared in monkeys against standard strains of poliovirus types 1, 2, and 3 No difficulty was experienced with the neutralisation tests and the viruses behaved like any other strains of poliovirus type 1

To exclude the possibility that the monkey antiserum to poliovirus type 1 which was used to identify each virus contained additional antibody to an agent other than poliovirus, a rabbit antiserum was prepared against the virus isolated from the intestinal contents of the bird at necropsy The rabbit antiserum neutralised the standard strain of poliovirus type 1 (Mahoney) maintained in this laboratory and also neutralised each virus isolated from the budgerigar The antiserum did not neutralise either type-2 or type-3 poliovirus

SUMMARY

Four identical viruses were isolated from three specimens (two of droppings and one post-mortem intestinal content) obtained from a budgerigar which recovered from a paralytic illness Each agent has been identified as poliovirus type 1 A similar virus was recovered from a boy who died of poliomyelitis which developed seven days after contact with the paralysed bird

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County Health Department, Hamilton
I C MONRO
M D Edin, D P H

Carluke
C C CUTHBERT
M B Glasg

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Malnutrition and Pathogenesis

AT a meeting in London on Feb 20, with Brigadier J S K BOYD, the president, in the chair, the relationship of malnutrition to pathogenesis was discussed

Prof B S PLATT said that it had long been known that the onset of beriberi was often related to a pathological event such as a non-specific bout of fever, and that many of the signs associated with malnutrition were non-specific and were due to non-dietary factors Malnutrition was disordered nutrition and was manifested by disturbances of growth, maintenance, and repair of the whole body or its tissues and organs, it might not always be due to dietary defects, but might in parts of the body be due to local disturbances of the circulation

Professor Platt related the general adaptation syndrome of Selye to malnutrition The effects of the stressor, which might be an infective agent, occurred in three stages alarm reactions, the stage of resistance, and the stage of exhaustion In these reactions the central nervous system and the endocrine system were fundamental Observations in Gambia indicated that protein intake would probably be adequate if it were not for anæmia and parasitism Infant mortality was very high, and this was probably at least partly related to low-protein diet, it was therefore important in the interests of the child to ensure that lactation was not ended too quickly, though lactation imposed a strain on malnourished mothers

Professor Platt cited experimental work showing that gastric ulcer and fibrosis of the liver can be induced by a diet poor in protein and that fatty livers can be produced by imbalance of hormones Arrested growth-lines in bones were common and could be related to illnesses such as measles and whooping-cough, which persisted longer if the nutritional state was poor, and these lines had also been found to be due probably to dietary inadequacy The importance of this conception of interrelationship between malnutrition and the stresses due to other causes was partly that in many malnourished communities more might be achieved by eradication of parasites than by increased food-supplies, and partly that attention should be given to the balance as well as to the level of nutrients

Dr G R WADSWORTH remarked that anæmia could not adequately be defined in terms of the hæmoglobin concentration of peripheral blood, but should be defined in terms of total hæmoglobin and metabolically active tissue The internal environment consisted of the vascular and extravascular fluids, the amount and composition of which were affected by endocrine influences, and derangement of these might be responsible for spurious anæmias in malnutrition On the other hand (as occasionally in pellagra) hæmoconcentration might mask true anæmia A body nutrient pool might be postulated into which absorbed nutrients entered, and which was drawn on during the various metabolic processes controlled by hormones Competition for nutrients existed between different tissues There might be circumstances in which the hæmopoietic tissue suffered and anæmia resulted but hæmoglobin formation seemed to have priority for available protein.

Dr L A. **Elson** described the effect of " butter yellow in promoting in rats cirrhosis of the liver and subsequent cholangioma and hepatoma, and the protection against such new growths provided by a high-protein diet Such protection was greater in a fast-growing strain of rats with a high capacity for tissue synthesis and repair than in a slow-growing strain A carcinogen with dietary deficiency produced conditions-favourable to cirrhosis and tumour formation, and this combination of factors might occur in Africa—the carcinogens were not yet known, though chillies had been incriminated in experimental work

Dr P M. **D'Arcy Hart** said that for protection against tuberculosis dietary protein was important Recent work in India indicated that chemotherapy might be as successful at first in the malnourished as in the well-nourished, but that for the development of bodily resistance to the disease adequate nutrition was essential A social and nutritional policy should be integrated with a programme of chemotherapy

Dr S **Bell** commented on the failure of adrenal function in anæmias observed in West Africa, and to experimental work indicating that corticoids had a protective action on the liver against injected toxic substances and also probably against other stress factors

ROYAL SOCIETY OF MEDICINE

Epidemiological Risks of Antibiotics

The Section of Epidemiology and Preventive Medicine met on Feb 21, with Dr **Ian Taylor**, the president, in the chair

Dr E. J L **Lowbury** said that the downward trend in the collective death-rate from infective and parasitic diseases had begun before the introduction of antibiotics, but had been steadier since, and for some (e g , erysipelas) the fall was initiated at that time The pattern varies from one disease to another, in some the number of notifications has stayed the same, or even increased, but the number of deaths has fallen The emergence of drug resistance had been noted in the last century, but with the use of antibiotics a new phenomenon was observed the prevalence of resistant strains and of certain phage-types of organisms in hospitals reflects the use of drugs there There have been reports of increased postoperative sepsis in late years, and the organisms are usually resistant to antibiotics, advances in, for instance, chest surgery, have been jeopardised It may be that patients with low resistance to *Staph aureus* are nowadays kept alive by other treatment, but there has probably been an increase in virulence, especially in staphylococci of phage-type 80

In the burns unit of the Birmingham Accident Hospital, patients are nursed in two open wards, though there are some cubicles and an air-conditioned dressing-station The organism giving most concern is the *Streptococcus pyogenes* because it usually causes grafts to fail; but staphylococci are also important, partly because some strains produce penicillinase and prevent penicillin from eliminating the streptococci (though no penicillin-resistant streptococci have been isolated) On several occasions, when a drug was introduced, resistant staphylococci emerged in a patient under treatment, and the proportion of resistant strains in the wards gradually rose, but when the drug was no longer used, the proportion fell, though at rates which varied from one occasion to the next This was true of tetracycline, erythromycin, and novobiocin The frequent appearance of resistant strains in patients who have been given none of the drug indicates cross-infection

Tetracycline-resistant streptococci of group A emerged in patients under treatment five years ago, and recently erythromycin-resistant strains have appeared, more than one serotype is involved Of the possible remedies, drug combinations (e g , erythromycin and novobiocin), though therapeutically valuable, have not prevented the emergence of resistant organisms, and aseptic technique must be improved

Answering questions, Dr Lowbury said that nasal carriers should probably be treated only when the strain present is of an epidemic type (e g , phage-type 80) or is causing a current outbreak of sepsis Significant resistance of *Staph aureus* to chlorhexidine (' Hibitane ') is rarely if ever seen In the treatment of nasal carriers, chlorhexidine is more effective if combined with neomycin He believed that when a given strain of organism becomes resistant during treatment, the mechanism of change which varies with the organism and the antibiotic, is sometimes a mutation, but usually replacement by a resistant strain In burns he has found that strains of *Clostridium welchii* are always sensitive to penicillin

Dr J B **Selkon** described a survey carried out in Britain by the Medical Research Council tuberculosis research unit to discover the incidence of resistant tubercle bacilli in untreated patients Sputum was sent to a central laboratory from 1404 patients in whom pulmonary tuberculosis had been newly diagnosed at 80 chest clinics Mycobacteria were found in 974 94 9% of the bacilli were sensitive to streptomycin, isoniazid, and *p*-aminosalicylic acid (P.A.S) Of the 44 resistant strains of *Mycobacterium tuberculosis* var *hominis* or *bovis*, 22 were resistant to streptomycin, 21 to P.A.S , and 7 to isoniazid The proportion of resistant strains was higher in women under 35 than in men or in older women, though the proportion of recent contacts was the same The explanation may be that clinical manifestation is more often due to recent exogenous infection in young women than it is in the other groups, if so, we may expect that in future the proportion of resistant strains in all new cases will be similar to that in this group (about 9%)

Dr H **William Smith**, of the Animal Health Trust, said that in veterinary practice resistance is most important in the strains of *Escherichia coli* causing diarrhœa in young calves and pigs (scouring) The frequent use of antibiotics in some herds has resulted in the emergence of a fæcal flora of *Esch coli* that is predominantly antibiotic-resistant , this has greatly complicated therapy About half of all pigs in Britain are now fed antibiotics, and at the bacon factories in 36% of the animals all the *Esch coli* strains isolated are resistant, and in 38% some are resistant When resistance appears in a herd after feeding of antibiotics, it tends to persist even when the drug is stopped The position with *Clostridium welchii* is different in that, though resistant strains appear, the organism is completely eliminated in some specimens from animals in which high concentrations of antibiotics have been fed

Among the speakers in the discussion was Dr MARY BARBER, who said that penicillinase-producing staphylococci were hard to produce in the laboratory, but she thought she had done so by exposing staphylococci to minute concentrations of penicillin for some years[1] The concentrations were similar to what might be expected in the air where penicillin was being used, or in tissues for very long periods after penicillin treatment

Reviews of Books

The Lower Urinary Tract in Childhood

S R KJELLBERG, N O ERICSSON, ULF RUDHE, pædiatric Clinic, Karolinska Sjukhuset, Stockholm Chicago Year Book Publishers London Interscience Publishers 1958 Pp 298 £6 6s

BASED on clinical and radiological studies of over 1000 children with disease of the lower urinary tract, this book will appeal not only to those engaged in pædiatric urology but also more widely, as a reminder of the possible role of organic lesions in urinary disorders in childhood It gives an impressive lesson in how to recognise these lesions by careful urographic investigation After an introductory section on embryology and normal anatomical development, the book is largely devoted to a series of cystourethrographic studies, with the incidental text often interrupted by several pages of illustrations The illustrations, however, demonstrating various obstructing lesions and their effect on the urinary tract, are so excellent that the book is well worth a place in the library of any radiological department

The Epileptic Seizure

COSIMO AJMONE-MARSAN, M D, BRUCE L RALSTON, M D, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 251 45s

DETAILED observation of the clinical and electrical accompaniments of an epileptic attack are all-important in diagnosis Opportunities to make such observations are greatly increased if attacks can be induced at will In this book the authors describe their experience with leptazol-induced convulsions in 119 cases They feel justified in submitting almost all seizure patients to this procedure " as part of their complete study "—a view with which most neurologists in this country would probably disagree They consider that the induced fits truly represent the spontaneous seizure, since in only 5% of cases did the leptazol produce attacks not clinically similar to the spontaneous ones

Having satisfied themselves on this point, they give their detailed findings, both clinical and electrical, of the aura, the fit itself, and the post-ictal phase, in these induced seizures The result is an extremely interesting and valuable contribution to the study of the epileptic process It is of interest to see how, as a result of such studies, the specificity of 3-per-second wave-and-spike activity in clinical petit mal is melting away The authors also record instances in which an undoubted clinical seizure was accompanied by no detectable change in the resting electrical activity of the cortex—an observation with considerable theoretical and practical implications

They not only attempt a correlation between clinical seizure patterns and the site of origin and progress of electrical abnormality, but they also use their evidence to suggest pathways of election for the propagation of the initial discharge to other parts of the brain The book could be made more useful by a slightly fuller index, particularly of the authors' own " shorthand " for various types of fit, and by page references to charts, &c, when they are referred to at a distance in the text These are small points, and, in general, the book contains much information important to all who have to treat epilepsy and to those who are interested in the way the brain works

The Story of Peptic Ulcer

RICHARD D TONKIN, M D, F R C P, senior physician to Westminster Hospital, London Philadelphia and London W B Saunders 1957 Pp 71 16s

THIS charming account of ætiological factors in peptic ulcers and how to handle them was born, the author says, of the tedium of endlessly repeating the same advice to countless sufferers It is illustrated by Ray Hellier's very humorous drawings After a single reading one is left with the feeling that one knows all about peptic ulcers and how to treat them The awkward complications of peptic ulcers are tactfully omitted The contentious question of ætiology is glossed over and the treatment recommended is uncomplicated and reassuring It would be interesting to learn whether patients find this short work helpful, it certainly seems worth a try, although the price is forbidding

Dr Tonkin has not apparently considered that his book might have a place in the teaching of nurses and medical students presumably it is not dry enough, and it might start a fashion for small-readable booklets which could present the essence of a subject in a highly assimilable form, so that students might master the important points in an hour's easy reading That might be one way of finally dispelling the view that medical teaching was meant to be dull and that students and nurses were born to suffer

Cardio-charting

Universal Method of Recording Heart Auscultation ARTHUR BRISKIER, M D, senior clinical assistant physician and cardiologist, Mount Sinai Hospital, New York City New York and London Macmillan 1957 Pp 58 42s

THIS is a beautifully produced and illustrated monograph of 50 pages about cardiac auscultation, and Dr Briskier rightly emphasises the need for some method of accurately noting the clinical findings Many physicians make a drawing of the sounds and murmurs with a grading of intensity, and to this the author wishes to add some musical connotations and different colours for sounds and murmurs Unfortunately he has not taken account of the considerable advances that have lately been made in the knowledge of cardiac hæmodynamics The third heart sound is attributed to ventricular contraction, presystolic murmurs are said to continue in the presence of atrial fibrillation, a calcified and narrow aorta is held to produce a loud harsh mid-diastolic murmur, and pulmonary stenosis is described as usually accompanied by a diastolic murmur By thus failing to keep his book in line with the latest observations in this complicated subject Dr Briskier has lost an opportunity to provide a practical guide that many cardiologists would welcome

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Handbook of Neurological Examination and Case Recording (Cambridge, Mass Harvard University Press London Oxford University Press 1957 Pp 114 22s)—In this revised edition, the general body of Prof D Denny-Brown's small handbook remains an excellent guide for the beginner The section on psychiatric examination seems long, especially since the author excuses himself from introducing new material on the grounds of space The supplementary investigations have a rather old-fashioned ring This is partly because of the absence of cerebral angiography space devoted to details of lumbar puncture and air encephalography (incidentally, how many clinics still indulge in complete air replacement?) could have been profitably sacrificed in favour of angiography The accounts of examination for aphasia, agnosia, apraxia, and perceptual disorders are particularly well done and will be useful to the practising neurologist as well as to the student

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THE LANCET
LONDON 8 MARCH 1958

Resistant Staphylococci in Hospitals

We are continually reminded that antibiotic-resistant staphylococci abound in hospitals,[1, 2] and that their prevalence and character constitute a perpetual danger of infection among both patients and staff[3–6] The latest such warning is contained in the striking report by Mr Slaney and Mr Brooke which appears this week on p 504 Nasal carriers of staphylococci among patients and staff have received a good deal of attention and the high proportion of them has possibly tended to create a feeling that their control may be beyond our present methods and resources It is interesting therefore, to find that Caswell et al[6] are a little inclined to question the role of the nasal staphylococcus carrier in the spread of infection within a hospital

In their hospital in February, 1956, there was a notable rise in the number of clean surgical wounds showing infection, and when accurate recording of the results was instituted the infection-rate was found to be around 5% Vigorous aseptic measures were instituted, and the rate of infection in clean surgical wounds fell to between 0 8 and 1 5%, at which it remained for the ensuing ten months About half the infections in this outbreak were found to be due to one phage type of staphylococcus, given as 42B/52/81, which is probably the same as, or a near relative of, the notorious types 80 and 81 At the same time as the outbreak of wound infection was observed, there was a sharp rise in cutaneous staphylococcal infections among hospital staff, and the two series of infections declined together Of the infections among staff, 64% involved forearm, hand, or face Members of the staff with infections were at once taken off duty and were not allowed to return until cured In this outbreak only 4% of 256 nasal carriers among a staff of 640 actually harboured the epidemic type of staphylococcus, which was responsible for 50% of the surgical wound infections, 76% of the cutaneous abscesses acquired by patients, and 80% of the typed staphylococci from hospital staff As regards the different possible means of spread of infection in the outbreak which they studied, Caswell et al[6] were more impressed by the importance of direct contact than of nasal carriers or airborne dissemination They refer to several instances in which certain areas of the hospital were free from infection with the epidemic type of staphylococcus until members of staff were found on duty with active infection with the responsible type McDonald and Timbury[7] recently showed how effective and dangerous a method of transmission this may be, and the same conclusion may be drawn from the observations of Barber and Burston[8]

Along with strict treatment of lesion-carriers among the staff, Caswell et al[6] naturally tightened all hospital aseptic routines, and (as they remark) it is difficult to tell which of these steps was the most important Jeffrey and Sklaroff[9] have reported that serious infection developed in 10% of 673 clean wounds in a hospital in this country It is vital that we should not come to accept rates of this kind as inevitable One important essential, no doubt, is to revert to the strict observance of aseptic methods which characterised the days before modern chemotherapy Clarkson believes that in the operating-theatre discipline has slackened in the past twenty-five years[10], and if it is true that the aseptic conscience of doctors and nurses has become less sharp, we are certainly in danger of doing great harm Also, notwithstanding the doubts expressed by Caswell et al[6] on the role of nasal staphylococcus carriers in their particular experience, it must remain an object of hospital practice to reduce their incidence Even a few carriers of an epidemic type of organism can give the organism a fair send-off on its way

Happily there is some new light on this problem On p 489 of this issue Dr Gould offers evidence on how hospital inhabitants may become carriers of resistant staphylococci He shows that there is substantial and widespread dissemination of penicillin particles in hospital air, and that the drug may be spread by droplets and dust In this way it will be inhaled by all who breathe hospital air, and may reach a high enough concentration in the anterior nares to eliminate the normal penicillin-sensitive staphylococci and so leave the penicillinised nose as a clear field for occupation by resistant staphylococci transmitted from the staff, many of whose noses carry such organisms Moreover, Dr Mary Barber has found some evidence that long-continued exposure of staphylococci to such minute concentrations of penicillin as may be present in air can lead to the emergence of penicillin-destroying organisms (see p 514) Dr Gould shows that penicillin was most abundant in the air of rooms where penicillin was being made up in solution or given to patients—that is, in dispensaries, wards, and outpatient treatment rooms Now that he has drawn attention to this undesirable contamination of hospital air with penicillin, there appears to be a good case for considering whether we should prepare antibiotic solutions, and clean the syringes with which they are injected, under cover of ventilated cabinets, such as that recommended by Williams and Lidwell[11] for handling infective material in laboratories Besides

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[1] Duncan I B R Collins A M Neelin F M Roy, T E *Canad med Ass J* 1957, 77 1001

[2] Petersdorf R G, Curtin J A Bennett I L, Jr *Arch intern Med* 1957 100 927

[3] Schwabacher H *Mon Bull Minist Hlth Lab Serv* 1958 17 23

[4] *Lancet* Feb 1 1958 p 250

[5] *ibid* Feb 8, 1958 p 301

[6] Caswell H T Schreck K M, Burnett W E Carrington E R Learner N, Seel H H, Tyson R R, Wright W C *Surg Gynec Obstet* 1958 106, 1

[7] McDonald S Timbury M C *Lancet*, 1957, ii, 863

[8] Barber M Burston J *ibid* p 578

[9] Jeffrey J S Sklaroff S A *ibid* Feb 15, 1958 p 365

[10] Clarkson P *ibid* Feb 22 1958 p 428 See *ibid* Feb 8, 1958, p 301

[11] Williams, R E O Lidwell O M *J clin Path* 1957, 10, 400

possibly increasing the number of nasal carriers of drug-resistant staphylococci, inhalation of penicillin bears *the risk of sensitisation* WELCH et al ,[12] as a result of a nation-wide survey of the U S A , have shown how serious a problem this is becoming, and have concluded that of all the antibiotics penicillin produces the most numerous and the most severe sensitisation reactions Nurses and pharmacists are perhaps exposed more than any others to this risk, but it should be added to the considerations which we weigh before prescribing any antibiotic

The responsibility for deciding whether to give an antibiotic, and which one to give, is rather often too casually delegated Bacterial infections in hospital and elsewhere are far more likely to be controlled by rigid asepsis, intelligent hospital organisation, thoughtful immunisation procedures, and rational chemotherapy than by the prevalent and ill-judged attempts to " hit the bugs hard " We should ponder the reproach of a man who in his day was one of our most active critics—the late GEORGE BERNARD SHAW [13] He deplored the coming of a generation of doctors " which having heard of microbes much as St Thomas Aquinas heard of angels, suddenly concluded that the whole art of healing could be summed up in the formula Find the microbe and kill it And even that they did not know how to do "

Blood-groups and Disease

THE idea that blood-groups may be associated with particular kinds of disease is not new[14], but except for the discovery of maternal-fœtal incompatibility as the cause of hæmolytic anæmia of the newborn, the findings were largely inconclusive until 1953 when AIRD et al [15] described an extensive survey of the distribution of the ABO blood-groups in patients with cancer of the stomach These workers found that in such patients blood-group A turned up significantly more often than in a comparable series of controls This result stimulated the search for other such associations The most striking to be brought to light was the relatively high frequency of blood-group O in patients with duodenal ulcer and to a lesser extent in patients with gastric ulcer [16-22] Associations have also been reported between group A and pernicious anæmia,[23] group A and diabetes mellitus,[24] [25] group O and pituitary adenoma,[26] group A and tumours of the salivary gland,[27] and group A and portal cirrhosis [28] A low frequency of group O has been noted in infants dying with bronchopneumonia [29] On the other hand no associations have been detected between the ABO blood-groups and cancer of the rectum and colon, cancer of the breast, cancer of the lung, and hypertension [16] [30-33] FRASER ROBERTS [14] concludes that the evidence for the association between blood-group O and both duodenal and gastric ulcer, and between blood-group A and cancer of the stomach and also pernicious anæmia, is exceedingly strong and that these associations are real He considers that, as regards most of the other reported associations, the findings, though highly suggestive, need further confirmation CAMERON [27] has since described a remarkable series of patients with tumours of the salivary tissues The association with blood-group A was pronounced, and this may prove to be the clearest association yet encountered

So far most of the work in this field has been concerned with the ABO blood-group system There are some data on the Rh system, but hitherto no clear-cut associations have been detected Little or nothing is as yet known about possible associations between particular diseases and most of the other blood-group systems, but CLARKE et al [31] have investigated the frequency of the ability to secrete ABH group specific substances in duodenal ulcer People can be classified into " secretors " and " non-secretors " according to the reaction of their saliva with reagents which detect the antigenic specificities peculiar to individuals of different red-cell ABO groups This difference is inherited independently of the inheritance of the ABO blood-groups, but is obviously intimately associated with them physiologically It was found that about 35% of patients with duodenal ulcer were " non-secretors ", compared with about 24% of controls

Each of the positive associations has been discovered by comparing the blood-group frequencies in patients with a particular disease with the frequencies in what was believed to be a random sample of the population from which the patients were derived The associations thus detected have usually been taken to signify that people with a particular blood-group are more susceptible to a particular disease than are others But there is another possibility A significant difference between the blood-group frequencies in patients and in controls might arise from some subtle differences in sampling due to unrecognised stratification of the population Thus if in a particular population there were two groups of people with different origins, one of whom happened to have a relatively high frequency of blood-group O and also a high incidence of duodenal ulcer, and the other a relatively high frequency of

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12 Welch, H , Lewis C N , Weinstein, H I , Boeckman, B B *Antibiot Med clin Ther* 1957, 4, 800

✓13 Shaw, G B Preface to The Doctor s Dilemma, p xxxiii London, 1928

14 Fraser Roberts, J A *Brit J prev soc Med* 1957, 11, 107

15 Aird, I , Bentall, H H , Fraser Roberts, J A *Brit med J* 1953, i, 799

16 Aird, I , Bentall, H H , Mehigan, J A , Fraser Roberts, J A *ibid* 1954, ii, 315

17 Clarke, C A , Cowan, W K , Edwards, J W Howel-Evans, A W, McConnell, R B , Woodrow, J C , Sheppard, P M *ibid* 1955, ii, 643

18 Brown, D A P , Melrose, A G , Wallace, J *ibid* 1956, ii, 135

19 Koster, K H , Sindrup, E , Seele, V *Lancet*, 1955, ii, 52

20 Heist, H *Tidsskr norske Laegeforen* 1956, 76, 10

21 Speiser, P *Krebsarzt*, 1956, 6, 344

22 Buckwalter J A , Wohlwend, E B , Colter, D C , Tidrick, R T , Knowler, L A *J Amer med Ass* 1956, 162, 1215

23 *Brit med J* 1956 ii, 723

24 McConnell R B , Pyke, D A , Fraser Roberts, J A *Brit med J* 1956, i 772

25 Craig J , Wang, I *Glasg Med J* 1955, 36, 261

26 Mayr, E , Diamond, L K , Levine, R P , Mayr, M *Science* 1956, 124, 932

27 Cameron, J M *Lancet*, Feb 1, 1958, p 239

28 Billington, B P *Aust Ann Med* 1956, 5, 20

29 Struthers, D *Brit J soc Med* 1951, 5, 223

30 McConnell, R B , Clarke C A , Downton, F *Brit med J* 1954, ii, 323

31 Buckwalter, J A , Wohlwend, E B Colter, D C , Tidrick, R T , Knowler, L A *J Amer med Ass* 1953 162, 1210

32 Walther, W W , Raeburn, C , Case, J *Lancet* 1956, ii 970

33 Maxwell R D H , Maxwell, K N *Brit med J* 1955, ii 323

34 Clarke C A , Edwards, J W , Haddock, D R W Howel Evans, A W , McConnell, R B , Sheppard, P M *ibid* 1956 ii, 725

blood-group A and a low incidence of duodenal ulcer, an association between group O and duodenal ulcer would appear to exist if the whole population was considered together, but might be not found to exist if each group could be considered separately. This is an awkward difficulty; but it can be overcome by comparing the blood-groups of patients with the particular disease with those of their brothers and sisters. By typing whole sibships a representative control is built into the investigation in such a way as to avoid sampling peculiarities due to unrecognised population stratifications. A positive association obtained in this way must certainly signify physiological interrelation of the two characters. Adopting this method, which is extremely laborious, CLARKE et al. confirmed their earlier finding that "non-secretors" of ABH substance are more frequent in duodenal-ulcer patients than in controls[34 35], but, in the 293 sibships studied, they did not confirm the association between duodenal ulcer and blood-group O.[34 36] This finding, however, is equivocal because (as FRASER ROBERTS has pointed out) the observed figures do not differ significantly either from those expected on the hypothesis that the association observed by comparing patients with separate controls is attributable to population stratification or from those expected on the assumption of true association. Further data should dispel this uncertainty. Meanwhile the association between blood-group O and duodenal ulcer has been observed in straight surveys carried out in centres as diverse as London,[16] Copenhagen,[19] Vienna,[21] and Iowa[22]; and it is difficult to believe that the same sort of stratification would occur in each of the very different populations served by these centres.

So far, except for the association between duodenal ulcer and "non-secretion" of ABH substances, no association has been confirmed by sibship studies. Nevertheless, it seems likely that at least some of them reflect true predisposition to disease. It has long been known that substances with A and B blood-group specificity are not peculiar to the red-cell surface: they can also be demonstrated in cells in most other tissues in the body, and they are often present in large amounts in the mucous secretions. It therefore seems reasonable to suppose that significant differences in predisposition to specific diseases may depend more or less directly on the particular character of these antigenically specific substances present in different people. Such a possibility is perhaps particularly likely in associations between blood-groups and conditions such as carcinoma of the stomach, peptic ulcer, and salivary-gland tumours, where lesions arise in regions where mucous secretions containing blood-group substances are formed. It has been suggested, for example,[37] that the presence of A substance in the stomach and duodenum may afford relatively greater protection against peptic ulcer, but rather less against carcinoma of the stomach, than do the other substances.

Besides substances which have A and B group specificity several other closely related substances are common in mucous secretions and in tissue cells. One of these is H substance, which is particularly prominent in people of blood-group O but may also be found in people of other ABO genotypes. H substance is thought not to be a specific product of the activity of the O gene, but to be a kind of precursor of the A and B substances. Nearly everyone exhibits A, B, or H serological activity in some combination on their red cells, and also in many tissue cells; but in only about 75% of people are substances with these serological properties present in the secretions. These 75% are said to be ABH "secretors", and the other 25% ABH "non-secretors". Whether a person is an ABH secretor is apparently determined by a pair of genes at a chromosomal locus independent of that which determines the ABO blood-groups. The situation is further complicated by the occurrence of another blood-group specific substance known as Le^a, the formation of which probably depends on a gene at yet another chromosomal locus. About 90% of people have Le^a substance in their secretions, and this seems to be true both for ABH secretors and for ABH non-secretors.[38 39] But Le^a-positive people who are ABH non-secretors secrete much greater quantities of Le^a than do those who are ABH secretors.[39] Thus nearly all people have one or more of these four kinds of serological specific materials in their secretions, and the particular ones present and their relative amounts seem to depend on genes at at least three independent chromosomal loci. Further studies of associations involving the ABO groups and specific diseases must ultimately include ancillary studies of the secretor/non-secretor differences and of the occurrence of Le^a in the secretions. This kind of information will be important in assessing any hypothesis relating predispositions to disease to the blood-group substances or their mode of formation.

So far little is known about the biosynthesis of these substances, but in the past decade considerable progress has been made, notably by MORGAN and his colleagues, in determining their chemical constitution. These workers have isolated substantially homogeneous preparations of the A, B, H, and Le^a substances, and have shown that they are all complex mucopolysaccharides with rather large molecular weights. The different substances resemble each other very closely in physical properties, chemical composition, and overall structure.[40] The clear-cut differences in antigenic properties are thought to be determined by relatively short oligosaccharide sequences, probably located at the periphery of the molecule. These differences are evidently rather subtle, and what is known about their chemical basis does not yet indicate how they may be functionally significant or likely to influence the development of pathological processes.

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[35] McConnell R B, Sheppard P M. Acta genet. 1956, 6, 574.
[36] Clarke C. A., Sheppard P. M. ibid. p. 570.
[37] Bentall H H. ibid. p. 566.
[38] Grubb R. Acta path. microbiol. scand. 1951, 28, 61.
[39] Ceppellini R. Congr. int. Trans. Sang. 1954.
[40] Morgan W. T. J. Lectures on the Scientific Basis of Medicine, 1954-55, vol. 4, p. 92. London, 1956.

Annotations

POLIOMYELITIS VIRUS FROM A BUDGERIGAR

THIS week we publish on p 512 a most unusual and tragic story Two budgerigars kept in the same cage became ill with a paralytic disease within a few days of one another The first bird died The second bird was recovering from paralysis of its legs when it was allowed out of its cage At this time it took hold of the lip of a 9-year-old boy by its beak, and held on to him until it was removed Seven days later the boy became ill, bulbar poliomyelitis developed, and he died Type-1 poliomyelitis virus was recovered from his stool The bird's droppings were examined two weeks and five weeks after the boy died, and at the time of the second sample the bird was killed and a sample of its intestinal contents taken From all three specimens type-1 poliomyelitis virus was isolated Dr Sommerville and his colleagues draw attention to the possibility of transmission of poliomyelitis by domestic pets, and the implication of their paper is that the budgerigars became infected with poliomyelitis virus, that one of the birds excreted virus for some weeks, and that the boy was infected by a bite from this bird This is not the only possible explanation for these findings, but any other explanation would require a series of strange coincidences to explain all the facts

Undoubtedly these findings merit most careful investigation In the past few years the epidemiology of poliomyelitis has been intensively studied, but no sound evidence has been produced that under natural conditions any animal other than man becomes infected with poliovirus It is possible, therefore, that the conclusion suggested by the report of Sommerville et al will be received with some scepticism Yet it is well to recall that not long ago poliomyelitis virus was thought to be strictly neurotropic, capable of infecting primates only It is now clear that it can be cultivated in vitro in diverse primate cells, and recently it has been grown in "transformed" cells of rabbit kidney [1,2] and of the chick chorioallantoic membrane [3] Some strains of poliovirus can also be passaged serially by the intracerebral [4] and intraspinal [5] routes in rodents, and in the chick embryo [6] There is therefore no fundamental reason why polioviruses should not infect budgerigars, although this property might be confined to only a few strains of virus If this can be established experimentally a whole new facet of the epidemiology of poliomyelitis will need to be reinvestigated

"EPIDEMIC PLEURISY"

IN 1955 the Turkish Army was affected by an epidemic of an unusual acute respiratory illness [7] There were 559 cases in a garrison force of about 2000, the incidence was greatest in March to June, and there was a further small outbreak in October to December The illness began suddenly with fever, malaise, cough, and slight sputum, which in almost half the cases was blood-tinged Fever lasted only four to five days, but the cough and other symptoms persisted, and few men were fit to return to duty under three months In every case there was a small pleural effusion, the fluid being sterile by the ordinary laboratory tests and the cells predominantly monocytes Intraperitoneal injection of the fluid into animals produced changes in the lungs—diffuse peribronchiolar infiltration with leucocytes and macrophages, and hæmorrhages Serological tests for Q fever and influenza were negative Less than half the patients could be radiographed, and in only 5% of these was the shadow of an effusion seen The lung fields otherwise appeared normal

The cause of the illness is unknown, but there was no evidence that it was tuberculous It differed clinically from Bornholm disease and "acute benign dry pleurisy" Apparently no other epidemics were present at the time, but it is not clear whether there were in fact no cases of similar respiratory illness without effusions The amount of fluid in the pleura was very small, and we cannot be sure that in other outbreaks of respiratory infections there have not been similar effusions, unless these were sought by thoracentesis

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[1] Sheffield F W, Churcher G M *Brit J exp Path* 1957, 38, 155
[2] Westwood J C N, MacPherson, I A, Titmuss, D H J *ibid* p 138
[3] Dunham W B Ewing F M *Proc Soc exp Biol, N Y* 1957, 95, 637
[4] Armstrong C *Publ Hlth Rep, Wash* 1939, 54 1719
[5] Li C P, Schaeffer, M *Proc Soc exp Biol, N Y* 1953, 83, 706
[6] Cabasso V J Stebbins M R, Dutcher, R M, Moyer, A W, Cox, H R *ibid* 1952 81 525
[7] Alptekin, F *U S Armed Forces med J* 1958, 9, 1

TOWARDS SAFER AORTIC RESECTION

CLAMPING the aorta can be dangerous, for several reasons Except where there is already a free collateral circulation, as in coarctation, complications in the spinal cord are caused by arrest of its circulation, the kidneys too are sensitive to any such deprivation of their blood-supply as would result from clamping the proximal aorta long enough for the surgeon to perform one or more arterial anastomoses Only when the lesion to be resected allows the upper clamp to be applied below the level of the renal arteries can the operation proceed without special measures to protect kidneys and spinal cord from ischæmic damage, or without an undue haste which is in itself dangerous

Fortunately, with the decline in late syphilis, thoracic aortic aneurysms are becoming rarer, but high-speed transport has brought a new source of aortic damage—the tear due to deceleration In most cases of traumatic rupture the tear is at the point where the arch joins the descending aorta, probably because the lower part, lying more freely, can jerk forward at the moment of impact [1] Teare [2] found this in nearly a third of the victims of an air disaster As with other arterial injuries, if the patient does not die at once from hæmorrhage an aneurysm may form, quite silently, over the ensuing months or years The condition will be recognised at routine chest X-ray examinations, or later when pain in the chest or other symptoms of compression develop Once aneurysm is diagnosed, surgical treatment must be offered, and this now consists in excision and arterial grafting

Attempts to reduce the danger to the spinal cord and kidneys at operation have taken various forms Lowering their metabolic needs by induced hypothermia has been tried successfully,[3,4] while the idea of maintaining the aortic flow itself by intubation [5] or shunt [6] has much to recommend it Extracorporeal circuits are now in fairly general use, as a means of providing rapid hypothermia [7] or of by-passing the heart itself [8] Gerbode et al [9] review thirteen published cases and add four new ones in which a pumped shunt was successfully used to conduct the circulation in the lower aorta One of the four patients died in the postoperative period from renewed hæmorrhage at the operative site, he had been given heparin and had required fairly extensive pleural dissection to expose the aneurysm The others all did well In these operations the shunt was placed between the left atrium and the femoral artery and was driven by a roller pump with manometric control of the inflow and outflow tubes, as well as of the systemic blood-pressure It functioned perfectly for 33, 45, and 55 minutes in the three patients who survived None showed any neurological or renal disturbance

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[1] Strassman G *Amer Heart J* 1947, 33, 508
[2] Teare, R D *Brit med J* 1951, ii 707
[3] Rob, C G, Eastcott, H H G *Lancet*, 1954, i, 573
[4] DeBakey, M E, Creech, O, Morris, G C *Ann Surg* 1956, 144, 549
[5] Hufnagel, C A Clinical Congress of the American College of Surgeons, 1948
[6] Clatworthy, H W, Varco R L *Proc Soc exp Biol, N Y* 1950, 74, 431
[7] Brock, R C, Ross D N *Guy's Hosp Rep* 1955, 104, 99

It is a real advantage to retain the normal body temperature in such patients in hypothermia the risk of ventricular fibrillation is ever-present, and it seems to be aggravated by high aortic clamping with its sudden strain on the left ventricle We may expect to hear more of this by-passing of the aorta while dissection and reconstruction proceeds in the unhurried way which is such an important factor in ultimate success

THE BURNING-FEET SYNDROME

THE burning-feet syndrome was observed in Japanese prison camps during the 1939–45 war [10] Malnourished prisoners had severe burning and aching in the feet, lower legs, and sometimes hands, without any convincing neurological signs The condition improved with administration of yeast and certain other substances containing vitamins of the B complex Gopalan [11] described the same symptoms in Indians, and reported rapid improvement with calcium pantothenate

A somewhat similar disorder is occasionally found in the old There are severe burning and aching in the feet, and less often hands, with no neurological abnormality and no apparent cause The symptom is worse when the feet are warm, and may therefore disturb sleep severely The burning pain in the hands which is so common a feature of "housewives' neuritis" is also mainly nocturnal and aggravated by warmth, but its ætiology is probably different

The burning-feet syndrome of civilian practice responds poorly both to pantothenic acid and to whole vitamin-B complex Bibile and his colleagues [12] provide further unequivocal evidence on this point In a simple but well-prepared and well-presented clinical trial they treated three groups of patients All had burning of the feet or other extremities as a prominent symptom, and none had any gross neurological, cardiovascular, or metabolic disorder One group were given 500 mg of pantothenol (the alcohol derivative of pantothenic acid) twice weekly by intramuscular injection, another group was given the same dose of pantothenol orally, and the third group served as a control Pantothenol had no significant effect on the symptoms

This well-conducted trial seems to absolve clinicians from the necessity of giving pantothenic acid in the search for a cure of this often distressing symptom A similar trial of whole vitamin-B complex is promised Judged by the sporadic results of clinical practice in this country the findings of this second trial may also be negative It is not unlikely, of course, that the syndrome seen here has a different ætiology from that seen in the tropics and in a setting of malnutrition, but there may nevertheless be some common biochemical pathway

CONSPECTUS OF ULCERATIVE COLITIS

ULCERATIVE colitis has been in the news since 1941, when the introduction of an adherent ileostomy bag gave an impetus to surgery, which in turn led to closer understanding of the pathology Intestinal obstruction is now recognised as the commonest complication following the institution of an ileostomy, it is usually due to fixation of the normally mobile small intestine by the stoma itself or adhesions leading to angulation and kinking, and the condition is prone to recur Garlock and Kirschner [1] ensure that the terminal two feet of ileum is fixed by plication in the position of their choice, hoping thus to avoid acute angulation Rogers [2] has reported two further cases of obstruction by obturation at the relatively indistensible stoma—or more exactly at the abdominal wall, since the exteriorised portion may become distended if the mucosa has been everted Impaction was brought about by a plum-stone in one case, and by a gall-stone in the other But patients with these stomas must be careful even with a normal diet plum-skins, like plum-stones, may lead to obstruction [3] Electrolyte losses from the stoma have been investigated by Crawford and Brooke,[4] who emphasise the sodium loss due partly to the voluminous postoperative output and partly to an increased concentration in the immediate postoperative period—though their figure of 300 mEq per litre is difficult to understand since it implies that the sodium level within the intestinal lumen is well above that in the plasma However, this figure has yet to be confirmed [5] From the Mayo Clinic [6] comes a report on pregnancy after ileostomy, from which Bargen et al conclude, albeit grudgingly, that it is safe for an ileostomy patient to undergo pregnancy provided that all the large bowel has been resected, for recurrence of colitis in a retained portion is, in their experience, the sole complication likely to alter the course of pregnancy

Thus the lot of the ileostomy patient is now much happier than of yore, but it is still not without difficulties and even dangers Dukes and Lockhart-Mummery [7] describe how these patients have taken some of the responsibility into their own hands by forming themselves into an association to aid new patients, to advise on problems of employment and reablement, and to promote research Perhaps the association's most valuable work is done through its visiting service, whereby hospital staff may call upon members to visit patients about to undergo operation, for nothing brings home more forcibly that an ileostomy need not cause disability than seeing someone with a well-established stoma and discussing problems and fears with him

Work on the ætiology of the disease has unhappily not advanced much [8] But in therapy conservative management has received a stimulus from the ubiquitous steroids

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[8] Kirklin, J W, Du Shane, J W, Patrick, R T, Swan, H J C, Wood, E H *Ann Surg* 1956, 144, 2

[9] Gerbode, F, Braimbridge, M, Osborn, J J, Hood, M, French, S *Surgery*, 1957, 42, 975

[10] Smith, D A, Woodruff, M F A *Spec Rep Ser med Res Coun, Lond* 1951, no 274

[11] Gopalan, C *Indian med Gaz* 1946, 81, 22

[12] Bibile, S W, Lionel, N D W, Dunuwille, R, Perera, G *Brit J Nutr* 1957, 11, 137

[1] Garlock, J H, Kirschner, P A *Surgery*, 1957, 42, 765

[2] Rogers, A G *Gastroenterol* 1957, 32, 343

[3] Brooke, B N *Lancet*, 1956, ii, 532

[4] Crawford, N, Brooke, B N *Ibid* 1957, i, 864

[5] Crawford, N, Brooke, B N *Ibid* 1957, ii, 340

[6] Scudamore, H H, Rogers, A G, Bargen, J A, Banner, E A *Gastroenterology*, 1957, 32, 295

[7] Dukes, C E, Lockhart-Mummery, H E *Brit J Surg* 1957, 45, 25

[8] Warren, R A, Berk, J E *Gastroenterology*, 1957, 33, 345

Kirsner et al [9] report that of 180 patients who received corticotrophin 85% showed immediate benefit, but 70% relapsed and the results of renewed steroid therapy were less striking From the circumstances revealed in the account of some of the cases it seems that not all the 180 patients had ulcerative colitis in the strictest sense, some may have had Crohn's disease, a condition more amenable than ulcerative colitis to steroid therapy Sleisenger et al,[10] who recommend corticotrophin in the fulminating disease, note that 'this may induce perforation, and Brooke [11] has shown that rapid "disintegration" may beset the colonic wall after administration of corticosteroids Though 3 of the 12 deaths in the series of 180 reported by Kirsner et al may have been due to perforation, Kirsner's group [12] have lately expressed the belief that in chronic ulcerative colitis corticotrophin does not increase this hazard But patients with chronic ulcerative colitis, though they may not be especially subject to this hazard, seem unlikely to benefit from corticotrophin, for Elliott and Carborne [13] have found, in a study of 30 patients, that steroids brought about *remission in no case* of more than two years' duration Otherwise there has been a description of a radiographic appearance (the indenture sign [14]) in colitis of any type, but particularly in ulcerative colitis This appearance seems to be identical with that previously described by Brooke [11] as pseudohaustration Finally Dennis [15] has reassessed vagal section undertaken in 30 patients eight to ten years ago Less than half had even symptomatic relief Of the 7 subsequent deaths 2 might have been prevented, as might carcinoma in another patient, yet alive, had excision, not vagotomy, been the choice

IDIOPATHIC PULMONARY HÆMOSIDEROSIS

IDIOPATHIC pulmonary hæmosiderosis has been recognised as a clinical entity only quite lately The basic anatomical lesion—deposition of iron-containing pigments in the lungs—was described by Virchow, but clinical reports did not appear until 1940 [16] In 1948 Wyllie et al [17] were able to trace only 17 published cases, but Soergel [18] recently reviewed 65

The disease affects predominantly children mostly but is also seen in young adults The age of onset is commonly 1–2 years, but a second peak occurs between 13 and 15 years [18] The characteristic symptoms are acute recurrent, and often increasingly severe, attacks of cyanosis, dyspnœa, cough, and hæmoptysis, other symptoms include vomiting, abdominal pain, fever, and tachycardia Attacks may last several days, and pallor and jaundice are usually evident before the acute episode ends The clinical signs indicate acute congestive cardiac failure, with tachycardia, distended jugular veins, a dilated right heart, congestion of the liver and spleen, and scattered moist sounds in the lungs [17] Macrophages containing hæmosiderin can be demonstrated in the sputum or gastric washings, children who swallow their sputum have occult blood in the stools Between attacks the child looks pale and weakly, fails to thrive, and suffers from frequent "upper-respiratory infections" Clubbing of the fingers and generalised lymphadenopathy have also been noted Hodson et al [19] describe two forms of radiographic change firstly, bilateral blotchy widely scattered shadows, up to 3 cm in diameter, which are characteristically transient and, secondly, slowly developing mid-zone and lower-zone miliary reticulation Comparison of the films of thin slices of lung with sections stained for blood and hæmosiderin showed the acute shadowing to be due to multiple small hæmorrhages, while reticulation was related to hæmosiderin deposits

Treatment is unsatisfactory and the average life expectancy is only three years from the onset Temporary spontaneous remissions are not uncommon, and must be taken into account in assessing therapy Improvement has been noted after splenectomy and after courses of steroids, and Browning and Houghton [20] report complete clinical remission for six years in an adult treated with corticotrophin

The ætiology is unknown Recurrent intra-alveolar hæmorrhage is followed by fibrosis The elastic fibres in the alveolar septa and small pulmonary blood-vessels are hypoplastic,[17] but it is far from certain that this constitutes the primary lesion The condition resembles the hæmosiderosis in mitral stenosis and cardiac failure, but the myocardial changes which are sometimes seen are insufficient to account for the pulmonary lesions The development of fibrosis depends on more than the presence of iron in the lungs, since it does not follow the inhalation of iron dust in industry [21] In hæmochromatosis the pulmonary lesions are inconspicuous in the presence of extensive fibrosis of the skin and other organs Similarly, in 16 cases of post-transfusional hæmosiderosis Kleckner et al [22] found that none showed significant iron deposits in the lungs It appears that intra-alveolar hæmorrhage is an essential prerequisite for the development of pulmonary hæmosiderosis

No disorder of the blood-clotting mechanism has been demonstrated in idiopathic pulmonary hæmosiderosis Reticulocytosis, a raised serum-unconjugated-bilirubin level, and increased urinary urobilinogen may simulate a hæmolytic process, but these findings are equally compatible with the destruction of extravasated blood The anæmia of idiopathic pulmonary hæmosiderosis is in fact of the iron-deficiency type, with hypochromia, microcytosis, low mean corpuscular hæmoglobin concentration, decreased serum-iron, and a favourable response to iron therapy This starvation in the midst of plenty appears to be due to inability to utilise the vast stores of iron contained in the lung parenchyma Using radioactive tracers of iron (^{59}Fe) and chromate (^{51}Cr), Apt et al [23] followed the red-cell survival and metabolic pathway of iron in 2 patients with idiopathic pulmonary hæmosiderosis Normal results were obtained during remission of the disease, but 1 of the patients studied during an acute attack showed an excessive plasma-iron turnover accompanied by high counting-rates over the lung fields which persisted for four months The red-cell survival was normal, and no excess of radio-iron could be demonstrated in the spleen These findings confirm the clinical and pathological evidence of intra-alveolar hæmorrhage, the cause of which remains a mystery

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Public Health

THE SURVEY OF SICKNESS, 1943-52

Was Our Survey Really Necessary?

STEPHEN TAYLOR

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England has been singularly fortunate in her medical statisticians. The official story started on July 10, 1839, when, by a piece of pure jobbery, Dr William Farr, L.S.A., was appointed compiler of abstracts in the new General Register Office at £350 a year. Had the post been formally advertised, this patient-less general practitioner might not have been appointed, Farr's Law might not have been enunciated, and we might never have gained what Major Greenwood has described as "the best vital-statistical system in the world."

In our own times, the Farr tradition has been finely carried on, under successive Registrars General, first by Dr Percy Stocks, and now by Dr W. P. D. Logan and his staff. But, though the tradition is the same, the tools are sometimes different. Among these new tools, an important place is occupied by the social survey and the technique of sampling. The story of what is almost certainly the most extensive health survey ever made is now told in the twelfth of the General Register Office studies on medical and population subjects—*The Survey of Sickness, 1943 to 1952*, by W. P. D. Logan and Eileen M. Brooke.[1] It is a story with more than a touch of adventure, with a romantic birth, a surprising confirmation, and a dramatic death. I know, for by good fortune I was there on each occasion in a godfatherly capacity.

The essence of the modern social survey is the technique employed at the point of collection of the data. A census may be made to yield facts of social importance, but the quality and control of the enumerators is inevitably variable. In a social survey, the investigator or his trained agents gather the field data under far stricter conditions. The first social survey in this sense was made by Dr John Haygarth in Chester.

> It was published in 1784, under the title of "An inquiry how to prevent the smallpox, and proceedings of a society for promoting general inoculation at stated periods." A careful field study of 20 smallpox cases showed that infection could invariably be traced to contact with another sufferer, and that provided simple rules of isolation were observed, there need be no further spread. Those observing the rules of isolation were each paid 10*s* reward, and the special thanks of the society are recorded to Mr Smith, watchmaker, and Mr Jenkins, tanner, who observed the rules but declined the money. The result of the survey was the establishment at the Chester Royal Infirmary of the first hospital isolation wards in the world.

The subsequent history of the social survey is unfolded by Dr Logan and Miss Brooke.

> To Edwin Chadwick, as secretary of the Poor Law Commissioners, goes the credit for the initiation of large-scale on-the-spot interviewing, as the basis for his report of 1842 on the sanitary condition of the labouring population. It was not until the end of the 19th century that Booth in London and Rowntree in York once more applied social survey techniques to the study of poverty and health.
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> The year 1912 was a landmark in social survey history, for it was then that Bowley, in a study of poverty in five provincial towns, introduced the technique of sampling. Instead of attacking every household, he interviewed only about one in twenty, selecting them at equal intervals from a complete list. This method resulted in a striking reduction in cost, with only a minimal and ascertainable reduction in accuracy. Thereafter, a spate of social surveys followed, among which were a number specifically directed towards health.

START OF THE SURVEY OF SICKNESS

In 1941, I found myself at the Ministry of Information, looking after the Home Intelligence Division and the War-time Social Survey. The Home Intelligence Division was a qualitative probe, designed to find out public opinion on the war and its effects among the civilian population. The War-time Social Survey was a precise statistical machine, for carrying out sample surveys at the request of any Government department. With a large team of interviewers, coders, sorters and statistical analysts, it could provide social and economic data about the habits and behaviour of the public as a preliminary to Government action. Speed was no less essential than accuracy, for Home Front decisions had to march in step with military necessity. So an interviewing team was built up large enough to sample the entire civilian population in a fortnight.

The birthpangs of the War-time Social Survey were violent. It survived the "Cooper's Snoopers" Press campaign and then a searching examination by the Select Committee on National Expenditure. Once it was safely established, the main difficulty was to maintain the organisation at concert pitch. *The field organisation could complete a survey in two or three weeks.* So the economic requirement was 12 to 15 major surveys a year. The Civil Service had to learn to use the new tool placed at its disposal. The task of keeping the survey going would have been far more difficult had not there been among the temporary war-time Civil Servants a sprinkling of university sociologists familiar with survey techniques and of advertising agents accustomed to market research. Perhaps one in four of the surveys made was literally vital to the war effort, as such, it was worth many times its cost. To get the one vital survey, three less essential but nevertheless useful surveys were needed to keep the wheels turning. In miniature, the position was that of an army which must always be ready to fight, yet able to spend only a quarter of its time in vital combat. So we had to become commercial travellers in social surveys, persuading colleagues in different Departments that accurate social diagnosis was an essential preliminary to successful treatment.

It was a happy paradox of the second world war that the gloomy expectations about health were not fulfilled. As Dr Logan and Miss Brooke remind us, food rationing, long hours of work, the blackout, and general stress and anxiety were expected to have serious effects on health. Yet 1942 broke all previous low records for maternal and infant mortality, stillbirths, and the standardised death-rate. The incidence of infectious disease was also remarkably low. Yet there were coming in many complaints of people feeling tired out, "below par," and "not up to scratch." Moreover, the reduced number of general practitioners claimed that their work had never been heavier. Here, then, was a genuine gap in the national health picture. The War-time Social Survey could provide a regular overall picture of the national morbidity, and conversely of the national health, obtainable at that time in no other way. Moreover, such a survey would provide the machine with the regular work it needed to keep it at concert pitch. Our offer to measure medical consultation-rates was quickly accepted by the Ministry of Health, and the War-time Social Survey went into action as an agent for the General Register Office to provide the raw material for a national index of morbidity.

The value to medicine of the Survey of Sickness can be judged from the report under review, and from the more detailed and specialised reports already published and listed in Dr Logan's bibliography The value of the Survey of Sickness to the Social Survey itself (it dropped the " War-time " from its title in 1945) deserves to be recorded

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[1] H.M. Stationery Office. February 1958. Pp. 50. 4*s*.

Since the war, the contribution of the Social Survey to national efficiency and the national economy in many fields has been enormous The peace-time Civil Service has used it wisely and well Yet without the Survey of Sickness as an important raison-d'être, the social survey might not have survived the stormy transition from war to peace

These were difficult days for politicians and Civil Servants alike Not only had a party Government, pledged to extensive social reform, to replace a Coalition, but also the war-time administrative machinery had to be reshaped or abandoned, and few knew just what was worth saving I was by then a new and green Member of Parliament Word reached me that the future of the survey was in the balance One powerful Minister was thought to favour its abolition So I sought him out To explain the value of sampling techniques in a semi-planned economy seemed a hopeless proposition So I told him that the survey was a continuation of the work of the Webbs, that it was in danger, and that only he could save it He agreed to talk it over with his officers and see what could be done He was as good as his word, and the survey in due course became a permanent part of the machinery of Government

TECHNIQUES AND COSTS

In its final form, the Survey of Sickness involved the monthly interview of a sample of 4000 people on the subject of their sickness experience during the preceding two months To cut down interviewer travel, a method of stratified sampling was used A specimen interview form or " recording schedule " is given in the report It is a beautifully clear document, designed to enable the interviewer to record with precision what might easily degenerate into a rambling account of past health experience Definitions adopted were equally precise, so that serious, moderate, mild, and minor illness have each a clear and continuing meaning

The appraisal of techniques in the report is full and fair and the conclusion that the memory factor was not a source of serious error seems to be justified The only criticism which can be made is the elaborate analysis of diseases alleged to have been suffered by the informants Yet even here, a sensible grouping of complaints into a number of categories commonly spoken of by the public has reduced what must have been a diagnostic jungle into a neat social plantation, which, even though its source was " what the patient said ", nevertheless has considerable medical significance

In one valuable table, diagnoses are related to average duration of incapacity and medical consultation-rates From this source it is possible to learn that there was one medical consultation for every ten attacks of the common cold, but three medical consultations for every two attacks of influenza

Some of the more striking causes of incapacity to work productively or domestically were

—	Average duration of incapacity in days per month per 100 people of 16 and over	
	Males	Females
Influenza	10 76	11 75
Bronchitis	9 56	9 15
Common cold	3 66	5 68
Cardiovascular disease	2 40	2 62
Rheumatism arthritis, and sciatica	7 31	8 33

These figures do not, however, include persons permanently incapacitated [2]

In all, between 1943 and 1952, nearly 300,000 people were interviewed At a guess, the cost of this investigation may have been about £30,000 a year It is virtually impossible to cost the conventional statistics of the national health, but it must be many times greater than £2500 a month There can be little doubt that the expenditure on the Survey of Sickness was fully justified The results are a quarry from which many have dug in the past, and many more will dig in the future, with great profit to the public health

SOME RESULTS

In precision, medical reporting has clearly many advantages over the direct survey of the public But it can never show the amount of morbidity and incapacity which does not reach the doctor's attention Out of 100 persons complaining of some sickness during an average month, 77 did not visit their doctor Though much of this sickness was probably trivial, the ascertainment of its extent and existence was possible in no other way

By good fortune, the Sickness Survey covered the period of introduction of the National Health Service Discounting the effects of the weather and influenza epidemics, comparing 1946–47 and 1949–50, there was virtually no increase in consultations for men under 65 For women and for old people, however, there was a real increase, leading to a total extra volume of work for the doctors of about 10%

The mean monthly sickness-rates over a six-year period show remarkably steady seasonal pictures In all age-groups over 16, females have higher rates than males, thus the figures for females aged 16–44 correspond closely to those for males aged 44–65

Among men, injuries cause between two and three times as much incapacity as among women, the average incapacity per injury being between four and five days A great part of this must be industrial injury of a comparatively trivial nature Skin diseases cause up to a fifteenth of all medical consultations though in those aged 65 and over, they form only a small part of the total illness recorded

The mean annual dental consultation-rate per 100 persons of 16 and over in 1950 was 51 for men and 59 for women Women had a higher rate than men in each occupation and income group Younger people see the dentist far more often than old people

—	Mean annual dental consultation-rate per 100 persons interviewed	
Age or occupation	Men	Women
16–44	63	81
45–64	36	41
65 and over	22	18
Professional and managerial	70	95
Agricultural	27	44

Perhaps the most illuminating figures of all are those for rates of medical consultations analysed by region

—	Monthly consultation rates per 100 people interviewed			
	Males		Females	
Age	16–44	45–64	16–44	45–64
Newcastle region	10	63	45	68
Manchester region	30	55	51	69
Wales	43	61	51	74
London	35	48	41	50
Cambridge region	20	13	34	13
Reading region	23	21	28	38

Such figures show the great difference in the number of consultations per patient at risk between the cold and damp industrial North and West, and the South and East

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[2] Varicose veins are not here counted as cardiovascular disease

They may help to explain the queues for general-practice vacancies in the South as compared with the paucity of candidates in the North.

CONCLUSION

The Survey of Sickness came to an abrupt end in February, 1952. Plans had been made, with the cooperation of a number of general practitioners, to check patients' statements at interview against doctors' records, but, before this could be done, the survey was stopped. The decision was taken at a high political level. Once more, I talked it over with the Minister concerned. But although he was satisfied that the Social Survey should continue as a piece of Government machinery, he declined to continue with the Survey of Sickness.

It must be at once said that his reasons were cogent. Other sources of national morbidity statistics were developing. The coming of the National Health Service had made possible a national hospital inpatient inquiry, the Ministry of National Insurance analysis of sickness claims gave a new and useful picture. And Dr Logan and his colleagues have initiated sample inquiries of general practitioners' records. Here we have in embryo medical intelligence service with greater potentialities than the Survey of Sickness.

As Dr Logan and Miss Brooke remark:

> “these, in their various ways, provide in greater detail and with greater accuracy, much of the information that could be provided by a Survey of Sickness, both as regards the volume and distribution of medically treated illness, and about its trend in time. There seems at present, while the statistical potentialities of these other methods are still being developed, no essential role to be played by a Survey of Sickness of the 1944–51 model, concerned as it was with the broad patterns of sickness in the adult population as a whole.”

With this conclusion one must concur. The Survey of Sickness was a good job, well done, of value in itself and of value in establishing the Social Survey. As long as the Social Survey and the Registrar General's office remain in being, they can come together again for ad-hoc or continuing inquiries, should the need once more arise.

Infectious Diseases in England and Wales

Disease	Week ended February			
	1	8	15	22*
Diphtheria	2	3	3	6
Dysentery	964	1060	1327	1545
Encephalitis				
Infective	3	3	5	
Post-infectious	2			2
Food-poisoning	145	163	158	188
Measles, excluding rubella	3473	3752	4533	4618
Meningococcal infection	26	37	42	35
Ophthalmia neonatorum	27	26	32	26
Paratyphoid fever	4	2	2	
Pneumonia, primary or influenzal	909	1023	884	793
Poliomyelitis				
Paralytic	4	16	13	15
Non-paralytic	7	4	5	10
Puerperal pyrexia	239	243	264	224
Scarlet fever	880	873	889	853
Smallpox				
Tuberculosis				
Respiratory	619	599	578	537
Meninges and C.N.S.	7	9	11	8
Other	56	59	71	50
Typhoid fever	2	2	4	2
Whooping-cough	645	721	580	645

* Not including late returns

The Widdicombe File

XLIV. “TOGETHERNESS”

DEAR ALVIN,

Many thanks for the reprint of your article on hypertension. I had already read it in the *PAJAMA* with admiration, even though I can't agree with some of your views on management. At least, I presume that they *were* your views, you chaps collaborate nowadays in such droves—I see you were fourth in the batting order—that it is hard to know who is responsible for which opinions. And don't tell me that even in the States six physicians can be found who all agree completely on the treatment of such a complex disorder as hypertension, because I just don't believe it! But possibly some of your collaborators just came along for the ride, so to speak?

However, over here as well, the fashion is all for “teamwork” these days. You can't attend a lecture or meeting anywhere without hearing someone hold forth on the virtues of teamwork and cooperation and liaison (when I was a boy “liaison” meant something quite different, but let that pass), and it all sounds very progressive and cosy. I suppose it is inevitable and in many ways desirable, though it does make the occasional oldfashioned individualist like myself feel a bit irritated at times. Desirable, that is, so long as the team is an association of medical men, but I seem to detect a growing tendency to want to bring the patient into it, and I think this can be dangerous.

Which brings me back to your paper and to that part of it with which I disagree most strongly. You advocate the practice of getting patients on hypotensive therapy to measure their own blood-pressures at home, and I gather that this is often done in the States. I don't think it is popular in this country—yet. “Physician–patient teamwork” you call it. Well now, it is obvious that in some fields of medicine like psychotherapy the patient's full cooperation is essential, and I agree that in diseases like diabetes you can't get really good results unless he is reasonably intelligent and helpful. On the other hand, sometimes the patient has to play a purely passive role, either because he is mad or because his disease is too complex and difficult for him to understand. But where I think we have to be careful with this patient cooperation business is in the diseases which have strong emotional overtones, and of these essential hypertension is an outstanding example. Tell the average patient that he has chronic nephritis or parkinsonism and he won't bat an eyelid, but tell him that he has poliomyelitis or high blood-pressure and you are liable to scare him stiff. Nobody fears uræmia, but everyone knows about strokes and heart-attacks. It seems to me that when you invite patients to cooperate in the treatment of their hypertension by recording their blood-pressure, you are asking them to adopt an impossibly objective attitude towards their disease, and then you run a big risk of aggravating the anxiety about it which nearly all of them already feel.

You may reply that it is all a matter of educating the public, and that I am just an insular old obscurantist, seeking to perpetuate an obsolete apartheid relationship between doctor and patient, in which the former dispenses esoteric magic which the latter must accept without question. I will admit that conditions are not quite the same in our two countries. Your patients seem to expect and even demand to know a good deal more about their condition than do ours. I have often wondered whether this is because British patients are intellectually lazier, or because they are not so sold on the wonders of modern therapeutics (though the B B C is doing its best in this direction even as I write) There is, you know, something to be said for not inquiring too much about what is going on, in case one should begin to have doubts as to whether it is likely to be successful However, to return to the point, there must surely always be a limit to the power of even the most intelligent and educated patient to understand his own complaint and therefore to his ability to cooperate, in the fullest sense of the word, in its treatment Moreover he can never view it dispassionately, as we do, because he is, to use current literary jargon, too much “ engaged ”

This isn't all jam for us Haven't we all at some time or another, when faced with a case whose management is proving difficult, been tempted to discuss our difficulties with the patient, and thus unload some of our doubts and anxieties on to him? And haven't we always bitterly regretted yielding even a little to such a temptation?

You are probably by now protesting that I am making very heavy weather of your comparatively innocuous suggestion that some patients be allowed to take their own blood-pressure Possibly I am, and perhaps I am wrong in seeing in this suggestion a straw in the wind, a step towards the “ Do-it-yourself ” Medical Kit, a move to shift on to the patient responsibility which is not rightly his to bear But patients put themselves in our hands, and it is *our* job to treat them, and *our* responsibility if we fail Suppose one of your patients muddles his measurements and things go wrong, don't you think you might be tempted—just a bit—to blame the result on him?

Sorry, Alvin, but I mistrust your “ physician-patient team ” notion It sounds fine, and in some circumstances may work very well But when dealing with disorders which are potentially fatal and for which we have not yet got a certain cure, it may, I believe, be harmful If you start taking patients into partnership, as it were, you will find that you are inevitably drawn more and more into discussing with them the pros and cons of what you are doing, and the chances are that you will finish up with a lot of very worried people

Tell me one thing Logically your ideal “ physician-patient team ” should be one in which the patient is himself a physician and can thus cooperate, team-up, or whatever with full understanding and insight Does therefore your heart leap with joy when you are asked to treat an anginal colleague? Well, all I can say is that mine doesn't I'll settle for the patient who says “ I leave it to you, Doctor ”, and who don't ask no questions and so don't have to be told no lies

I shall expect an I C B M by return of post Meanwhile, love to Susie and Alvin junior Young Rodney says can you possibly send him a real satellite for his birthday? One of the very small ones would do The poor child suffers from a fixed delusion that doctors have something to do with Science!

Yours transatlantically,
RODNEY PEARSE

Special Articles

PSYCHIATRY IN GENERAL PRACTICE *

H STEPHEN PASMORE
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IT has been the tradition in hospital for disease to be considered either organic and worth investigating or functional and not worth investigating Functional disorder has therefore seldom been properly evaluated, and practitioners who “ reassure ” their patients that there is nothing wrong with them except their nerves remain unconscious of the fact that they are reassuring only *themselves* that there is no underlying organic disease

Functional disorders cannot be investigated by the methods applicable to organic disease The doctor who chooses to investigate functional disorder needs to keep a quiet, patient, and receptive mind during the interview with his patient, and must find time for the work outside his busy surgery hours Clearly investigation by question and answer, or by X-ray or other precision instrument, will tell the doctor nothing about the patient's mental problem The unconscious does not present itself dressed up in the language the student is taught to use at hospital when investigating organic disease It has a special language of its own which has to be learnt Unfortunately, though the words are the same, the way they are spoken and used is different The doctor can therefore investigate functional disease only by learning this language and listening to what the patient has to say or to what he is trying to say

What is the language of functional disorder? Let us consider the words of a patient

“ I want an X-ray,” he says It is natural for the doctor to assume that the patient is using the word “X-ray” in the same sense that he uses it himself So when the patient goes on to say that he has been living with his brother who has been found to have active tuberculosis, the doctor considers the patient's request a reasonable one and arranges for him to be radiographed

But there is another type of patient who asks for an X-ray of his chest He comes into the surgery rather nervously and says, perhaps, that he has a vague tightness on the left side of his chest and that he is afraid he might have cancer The doctor immediately senses something “ functional ” about this He takes a careful history and examines the patient thoroughly “ My dear chap,” he says, “ I can't find any sign of cancer Your heart and lungs are quite healthy There's no need for an X-ray In fact, no need to worry at all ” “ But I would like an X-ray, doctor,” the patient persists And the doctor, looking at his notes, says “ But I see my partner sent you for an X-ray only three months ago and nothing was found wrong then ” “ I know,” the patient continues pathetically, and at the same time rather obstinately, “ but I should like one all the same—to make quite sure ” And it is at this point that the wretched doctor usually gives in, either because he now can't feel quite sure himself or because he wants to get on with his surgery

But why doesn't the doctor listen to the patient? In the first case he listened carefully and carried out the patient's reasonable request In the second he knew the patient's demands were unreasonable, but as soon as he became aware of their large functional element he lost interest, and was no longer able to observe or listen to the patient carefully He started to impose his own personality between himself and the patient He let his mind wander on the subject of neurotics in general and the man's obstinacy in particular, and naturally became unaware of what the patient was trying to say

The patient was clearly under some stress, which was oppressing him He felt uneasy and tight about the chest He must seek some relief from this sense of oppression He would go to his doctor But his doctor would laugh at him if he just said he had a tight feeling in his chest Of course, it had come on only after his wife had died, but he didn't suppose that would have anything to do with it He had never felt ill before If only his doctor could find out what was the matter with him See through his trouble That's it! I'll get him to X-ray me Good heavens! There was that awful article about cancer of the lungs and smoking Yes, I must see the doctor and get an X-ray I may have got cancer

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* From a paper read in a symposium on this subject held at University College Hospital, London, on Oct 18, 1957

The doctor should change his technique of investigation in a case like this, as soon as he senses the functional element He should stop asking questions and let the patient tell his story in his own way And if the patient can then feel that the doctor is sympathetic to what is going on in his turbulent mind and is making no attempt to pass a moral judgment, he will tell the doctor far more about his real problems—more about his unhappy domestic situation than about the tightness in his chest But at the end of the first interview he may well return to the attempt to blame his symptoms on some organic disease

In general practice at least 40% of patients have symptoms of functional disorder, and as most of them are investigated for and treated with remedies for organic disease, it is not surprising to find them attending regularly year after year Doctors cheerfully accept this anomalous situation till the anomaly is pointed out to them, and then they cannot understand how they ever came to accept it Let me give a simple illustration of the change that has taken place in my practice since this anomaly was pointed out to me by Dr Michael Balint in his general-practitioner group at the Tavistock Clinic

A married woman, aged 24, rang me up one morning from her office saying that she had collapsed on her way to work with palpitations of her heart, that she felt better now she had rested, and would I see her? As she spoke, I came to the conclusion that she was not suffering from organic disease (such as the onset of auricular fibrillation) because of the words she used to describe her symptoms And I must stress here that analysis of the language the patient uses gives the clue to his problem every time, or perhaps not so much analysis as automatic recognition of the words and phrases used Five years ago I should have taken her history, and she would have said, as she did, that she felt faint while walking from the bus stop to her office and had felt a sort of flutter in the front of her chest, that she had been helped to the office and had recovered in a quarter of an hour after resting quietly in a chair I should have thought to myself, as I examined her, of such possibilities as a minor epileptic fit, heart-disease, or early pregnancy I should have found nothing physically wrong I might have referred her to a cardiologist to exclude heart-disease, or to a radiologist to exclude early pulmonary tuberculosis I should then have reassured her that there was nothing wrong, that young people like her occasionally felt upset like that, and that she should report again if she had any further attacks In fact I did none of these things From the opening conversation on the phone I sensed that the problem was an emotional one, and when I saw her I decided to listen carefully to what she had to say and direct any questions that had to be asked to finding out what was happening in her mind at the time of the incident

"I got off a bus in Oxford Street yesterday morning, and while walking to the office felt a sudden flutter in front of my chest"

'Were you walking with anybody?'

"Oh, yes, with another girl from the office, and she said 'You look pale', and then I realised my heart was thumping and I felt I was going to faint But she helped me get to the office where I sat down in a chair till I felt better

'But what were you talking about?"

Talking about? Oh, I remember It was about the Bank Holiday weekend"

Yes but what about it?" (You will notice the patient was putting up some resistance here. That meant I was getting warmer but was on dangerous ground, and if I pressed my inquiry too hard the patient would get frightened and say nothing of importance)

"Well, she said she had to go a long way to visit her parents, and I said that fortunately mine lived fairly near and that I was going to visit them on the Sunday and my husband's parents on Monday, and then I felt the flutter"

She went on to say that she had been happily married for a year, that she had no particular worries, and that she got on as well with her husband's parents as she did with her own But then she volunteered the remark that her in-laws ran a pub, and from the way she said the word "pub", it was evident that either she did not like her in-laws as much as she pretended to herself she did, or she could not bear to be associated with anyone who ran a pub It was not surprising, therefore, to find that in suppressing her natural dislikes and pretending all was happy she should convert her strong unconscious feelings about in-laws and pubs into a respectable cardiac palpitation I interpreted this to her and it obviously struck home, for instead of saying "Is my heart all right?" she said "What shall I tell my husband?"

Now do let me be clear over this case I did not cure the patient I merely found an explanation for an apparently non-organic irregularity of the heart-beat It would need many more talks with the patient to make her feel less upset by her in-laws' connection with a pub What did a pub mean to this patient? Why not something quite respectable? And so on But in this case I think the patient felt quite clearly the connection between her faint attack and her in-laws, and as a result would be unlikely to have a further attack I say "felt clearly", because it would not have been enough for her merely to have listened to my explanation of her problems, for to say to a patient "It's only your nerves" seldom convinces them of the truth of your remark or makes the slightest difference to the alleviation of their symptoms

When we listen carefully to what the patient is trying to tell us we often discover, early on in the conversation, some significant fact which seems to explain everything, but the rational explanation the patient first puts forward to the sympathetic doctor is seldom the real explanation of his trouble We must therefore be cautious in interpreting the patient's first significant remarks as denoting the cause of his disorder

An intelligent, but nervous, young secretary consulted me about a sudden feeling of weakness in her legs, and told me she thought she might be getting "polio" I examined her and said I could find nothing physically wrong She said she was glad to be reassured as she thought she might have caught it from her cousin, when she had visited him in hospital and found his legs paralysed She had been dreadfully worried about her cousin I then explained to her that her anxiety and the weakness of her legs were a natural and direct result of the worry over her cousin, and thought that my reassurance would be sufficient to restore the strength to her legs But two days later she asked me to visit her as she felt too weak to come round and see me I called to see her and again had to reassure both her and myself that she was not developing "polio", but I still had to continue my visits and it was only at the fourth visit that she blurted out that she could not understand why she had given in to this nervous illness since she had coped so adequately with a much more distressing problem three months previously, when her fiancé had broken off their engagement, leaving her alone and insecure

It then became clear that this broken engagement was the significant factor in her breakdown, and that, though she had apparently shown no outward signs of distress at the time, she had eventually given way as a result of the undermining influence of her cousin's illness It became clear that her fiancé's rejection of her had given her a sense of instability, of which she felt ashamed, and that when circumstances offered her the possibility of poliomyelitis being the cause of that instability she readily accepted it

It is necessary for us to be more sensitive to the disturbances of the unconscious It is not enough to replace a label of "fibrositis of the shoulder muscles" with one of "a psychomatic disease due to constant muscle tension in a nervous person ", when no underlying organic disease is present We must go deeper We must listen more carefully to the language the patient uses to describe his complaints and note the order in which those complaints are presented We must note the choice of phrase and the use of colourful adjectives We must note the moment of hesitation or silence, and the moment of laughter or tears We must remember in a first interview that the words that really matter are often the last words the patient says as we are writing out the prescription or seeing him out of the door These are the words, often spoken half jokingly, which express his real fears and which are said last only because he knows that if you laugh at him he can make a quick exit without appearing more foolish than he feels for having said anything at all We have all heard the patient say, after a long examination that has proved nothing organically wrong, " Well, you don't think I am going to die, doctor, do you ? " and we have said, " Of course not I wish I were as healthy as you ", when we ought to have said, " Let's start this interview all over again What on earth are you really frightened about ? " This is the moment when the patient is most ready to tell us his troubles, and the moment when we are least ready to listen to them

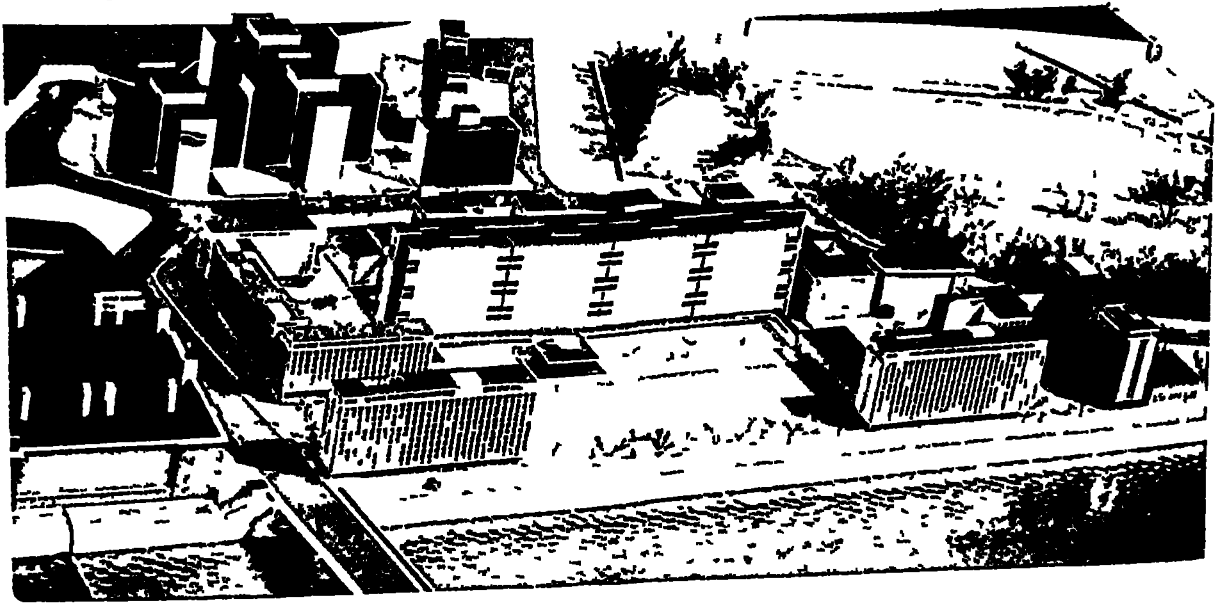
We must take our time We must never interpret to the patient too quickly what we think is the matter with him We must establish our relationship with the patient, not by showing him how kind we can be, but by showing him that we know what is going on in his mind and that we are not making any attempt to pass a moral judgment on what we find We must always let the patient work his problems out in his own way If the patient asks for advice, we must forbear the temptation to give it We shall get much better results if we throw the words back and say, " Well, what would you do ? " or " What do you think about it ? " We must remember that many of these patients have had a difficult background and are playing out a predestined pattern of behaviour—a pattern related to their failure to work through the facts and fantasies of their early relationships with their parents in the œdipal situation We must also recognise that our own reaction to the patient can be interpreted as a symptom of their illness For instance, if at the end of an interview with a mildly hysterical woman we feel we are in a complete fog and cannot get any clear picture of her problem, we can be sure that that is just the situation in which the patient finds herself—in a complete fog

We can learn to unmask the disturbances of the unconscious mind that masquerade as organic disease only by studying the language of the unconscious, the language of symbols and silences, fears and fantasies, paradoxes and half-veiled truths If we claim to treat all the patients who seek our advice, we must examine not only the organic parts of the body but also the fantasies of the mind Only then can we come to a clear decision whether we can handle the patient's problem ourselves Only then can we know where to refer the patient if his problem is beyond our skill

REBUILDING ST. THOMAS'S HOSPITAL

The Minister of Health has agreed that the governors of St Thomas's Hospital, London, shall proceed with the initial stages of planning the new hospital on the lines we described in January [1] An illustrated booklet [2] outlines seven schemes that have been proposed and rejected, and an eighth which has been adopted This scheme entails the diversion of Lambeth Palace Road to run 400 feet further from the river The accompanying figure shows what the proposed hospital would look like from the north-west In the centre is the main eleven-storey ward block with laboratories, the outpatient and operating-theatre block lies behind it Nearer to the river and to the left are gardens and residential blocks for staff, on the extreme right is the medical school On the extreme left is County Hall, the buildings in the background, between the hospital and the railway, are not part of the hospital but are on a site owned by the governors

The structure will be entirely new, except for three buildings (St Thomas's House, Riddell House, and a post-war laboratory) near the medical school The Royal Fine Arts Commission has approved the scheme in general, with some reservations about the medical school building but none about the hospital itself The scheme will be submitted formally to the London County Council, the planning authority



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[1] See *Lancet*, Jan 11, p 113

[2] Proposal for the rebuilding of St Thomas s Hospital, 1957

In England Now

A Running Commentary by Peripatetic Correspondents

WHO that saw it can forget (unfortunately) the recent feature starring Mr Roderick (Butterfingers) MacGrolloch and his appendicectomy troupe. We easily recognised Mr MacGrolloch because his theatre gown was inside out, and on the back were his name, address, telephone number, consulting-hours, and the nearest tube station. His personality came across vividly in his preamble. The shock was intensified when we learned the operation at which he intended, to quote his Doric colloquialism, "tae hae a baaash". In contrast with the mutilating operations which remove the appendix "in toto parrrrentis", said Mr MacGrolloch, his multi-stage appendicectomy for surtax payers is the teeniest possible pruning of the annual growth of the organ. As he put it "You trim your hair, nails, and front lawn. Why not your appendix?"

The camera then took us into the theatre. There was brilliant symbolism in the opening panning shot, whose vertiginous nystagmus resulted from the theatre orderly's efforts to get the camera trolley off his foot, and for the next twenty minutes the viewers were gripped by the drama of a life-and-death struggle in the operating-theatre. Then the anaesthetist remembered to turn on the gas and the operation started. Mr MacGrolloch used his sensational "treble chance" approach, which necessitates three incisions, one for each of his team. They can thus remove simultaneously three organs, one of which may well be the one they want.

The last thing your correspondent remembers was the supine patient and Mr MacGrolloch hefting his scalpel like something out of *Moby Dick*, but viewers who retained consciousness will be glad to hear that the technician who fell from the camera-boom through the theatre skylight rapidly recovered when removed from hospital.

Credit should be given for the imaginative close-ups showing the anaesthetist's hands relentlessly suppressing the patient, pouring the tea, and catching up on his mail—though I still think he should have put Arsenal down for a draw. Then on to the other camera to watch screen-stealer MacGrolloch do a breathtakingly difficult dissection of two indispensable pages of *Surgical Handicrafts*, which had got stuck together with brown ale.

Altogether a memorable evening, and sucks to the old fuddy-duddies in Tavistock Square who don't want us to know when we're developing appendicitis.

* * *

On Feb. 25 a man was admitted to our wards with a head injury. He had been watching the heart operation on television. When the heart was opened he fainted and hit his head on the floor. Now we are awaiting a patient with a heart attack resulting from watching the forthcoming head operation to complete our studies of this fascinating new field of traumatology.

* * *

"I know just the thing", he had said. His face had lit up with the pleasure of being able to help. I had poured out all my symptoms as rapidly as I could—lack of sleep, loss of appetite, constipation, palpitation, giddiness, blackouts, and many more—and he had examined me first from one side of the bed and then the other. Perplexed and flustered he had stood back, and I had mentioned THE PAIN. There was no doubt my story was odd and my signs, if any, were no doubt odder but here was something to be grappled with and laid low. I had a pain, not perhaps a severe pain or even a moderate pain, but certainly a pain. "I know just the thing", he had said and he had written out the prescription with a gleam of satisfaction in his eye although there was still an anxious look on his face and a certain reluctant resignation as he left me and my symptoms to myself.

Now he faced me again. "Did they suit you?" he asked. I lay there, miserable and wretched patient that I was. What should I say? His prescription lay untouched, in the top drawer. He had a worried expression. His eyes were looking at me full of doubt, full of apprehension. In anguish he gazed at me. In anguish I gazed back. "Did they suit you?" he asked. I screwed up my courage. I knew his symptoms I must treat him, but my own symptoms lay like a pall over me, impeding me. The corner of his mouth quivered, and I knew that I must act quickly. "They were wonderful", I breathed. His face relaxed and it was as if day had dawned after the night, as if peace had come after war. He squared his shoulders. His face relaxed and became assured. He felt my pulse. I closed my eyes and dropped into a deep calm sleep. I went back to work next day and he hasn't needed to see me any more.

* * *

The fact that there's a hedgehog at the bottom of our garden does not seem inherently remarkable, until you realise that our garden is in London, N.7, with close on two miles between us and the nearest major open space. I first spotted him (or her) late one evening in September, in the gutter outside our front door. By the time I had collected the family and a coal-shovel, he had gone. But ten days later he was there again. This time I collected the shovel only, and just managed to beat him to it. I popped him down on the garden path, shut the gate, and only then called the scrutiny committee. By this time he was already halfway across our garden. It is always a surprise to see a hedgehog run, and I have yet to see one climb, a feat they are said to perform when in search of apples. Anyway, that was the last of our hedgehog, for he was seen no more.

Last Sunday I was digging out compost when I noticed something strange in the wheelbarrow. It was a touch of spring, a fresh grey-green, quite unlike its very dead surroundings. It was the hedgehog right enough, in, I presume, hypothermic coma, unless my shovel had done him some mortal injury. Mindful of the story that the hedgehog is fuller of fleas than a fowlhouse, I did not carry out a full physical examination, but quickly made him a new bedroom on the safe side of the compost heap. I hope I buried him deep enough, for two days later he was under eighteen inches of drifted snow.

* * *

Recently an anæsthetist friend sat one of the higher examinations in anæsthetics. He was questioned among other things on the breakdown of hæmoglobin in the tissues, the tissue reactions in acute and chronic inflammation, atrophy and necrosis, the biochemical processes involved in the absorption of iron, the reactions of the body to septicæmia, and antibiotics. It seems to me that had my friend passed this examination he could reasonably have been described as a competent pathologist and biochemist practising in anæsthetics.

If the examiners really wish to introduce extraneous subjects I would like to suggest something more relevant, such as the advanced driving test to ensure punctual attendance by the anæsthetist, or, to the same end, the ability to fly a helicopter.

* * *

First chronic in medical ward. Did you hear that we had a case of syphilis in yesterday?

Second chronic. Thank heaven for that. I'm tired of these glucose drinks.

* * *

The physicians and the psychiatrists are peering at each other across the hypothalamus.—R. Cobbleigh (*Lancet*, Feb. 8, 1958, p. 310).

The G.P.s and the Consultants
Were gathered in a band
They talked like anything to try
Their cures to understand.
"If this were only done,' they said,
"Why—treatment *could* be planned!'

"If seminars and symposia
Can't make it clear to us,
The principle" the Doctors said,
"Remains anonymous.'
'Well—call it", said Psychiatrists,
"Just Hy-Po-Thal-A-Mus.'

Letters to the Editor

LONG-TERM ANTICOAGULANT TREATMENT FOR CORONARY-ARTERY DISEASE

SIR,—The enthusiasm for long-term "anticoagulants" in your leading article of Feb 22 makes the unconverted feel like a pagan sinner We are plagued by confusion Honey and Truelove's careful study is swept aside with the implication that its facts are embarrassing to the point of indecency The correspondence that followed its publication was in fact longwinded and tendentious, and even suggested a vested interest in the continuation of "anticoagulant" control By selective quotation your leader sounds convincing, but it ignores a great deal of evidence, such as the criticisms of much American work by Rytand,[1] or the insignificant differences in frequency of thromboembolic complications noted by Manson and Fullerton,[2] though the latter had a higher mortality in their controls perhaps due to a greater proportion of patients over 60 in this group Your leader fails to comment on the extraordinary discrepancies between Keyes' work and that of Bjerkeland [3] Keyes noted a fivefold reduction in death-rate in patients with recurrent infarction, but Bjerkeland found little significant difference between treated and untreated in a similar group of patients over the age of 60 anticoagulant treatment did little to affect mortality Surely in the older age-group at greater risk effective preventive measures should be seen at their best Mortality in reported untreated series varies enormously from 13% to 45% [4] and Toohey's comparison of his treated mortality with *Honey and Truelove's control series* would hardly satisfy a statistician

But since there is no real evidence that the antiprothrombin group of substances stop or even significantly delay intravascular blood-clotting, perhaps they act in another way Wright and Kubik [5] suggested that they could accelerate recanalisation of thrombosed veins and arteries Yet Manchester found postinfarction angina equal in severity in treated and untreated patients

No, Sir, bitter experience of progressive coronary clotting under our very eyes with optimal "anticoagulant" control leaves us unconvinced that the evidence is as yet adequate to justify vast expenditure on "anticoagulation" services While anxious to do the best possible to tip the balance even slightly in favour of our patients, let us preserve balanced and critical judgment Coronary-artery disease presents a spectrum of great width from minimal atheroma with perhaps an unlucky clot at a vital point causing sudden death, to gradual pipe-stem narrowing over decades with hardly a symptom Occlusion may be thrombotic or due to subintimal hæmorrhage We have the Duguid view that thrombosis causes atheroma Others would have us believe that the diet of the Bantu will save us, but the Pietermaritzburg pathologists, Laurie and Woods,[6] think there is as much atheroma in the Bantu as in Barts

Strong emotional devotion to corn-oil diets or anticoagulant pills will do no good to medicine Only the most extensive carefully controlled trials on a national scale such as that organised by the Medical Research Council may give us some sort of answer, but only if it is realised that coronary-artery disease is almost universal especially in the male population over middle age, that occlusive clotting is an accident taking place in a few moments on a disorder of the vessel wall which lasts for decades this accidental concatenation of circumstances accounts for the great variability of course and mortality which seems to baffle many earlier attempts at statistical analysis Clotting may occur at times of stress, physical or mental, and the reassurance and care of a good doctor may be just as important in its prevention as "anticoagulant" pills

Postgraduate Medical School,
London, W 12 JOHN MCMICHAEL

SIR,—Your leading article is indeed timely in view of the increasing use of this treatment and the encouraging results reported My preliminary results in a hundred patients have been very promising and I hope to report on this trial soon Meanwhile, I should like to comment on a few of your points

You rightly say that patients are likely to find it irksome to have blood samples taken every few weeks In all published results so far the maximum interval allowed between blood-tests is 3 to 4 weeks I have always thought that, where a treatment has to be maintained for years, it is too much to ask patients to attend every few weeks, particularly when they are at work or have to travel a good deal, and, as you mention, with increasing numbers being treated the strain on the hospital services becomes enormous For these reasons therefore our aim has been to maintain effective control with blood-tests taken at intervals of no less than 2–3 months, and it has been found perfectly feasible to achieve adequate anticoagulant cover without serious mishaps with such infrequent tests The minimum period between tests for the few patients who are difficult to control is 4 to 5 weeks, but about 90% attend every 8 to 12 weeks This interval enables patients to live with a minimum of interference, and means smaller clinics, so that more individual attention can be given to each patient Except for isolated cases a "postal service" is to be avoided, because the patient must be instructed personally in any change of dosage and in other details of the treatment, even written instructions can be misread, as I have learned by experience

There is a further very important point too-frequent blood-tests can in fact be misleading and cause inadequate control The variation between the maximum and minimum maintenance dose in nearly all patients is so small—about 2% to 3%—that the effect of such small changes in the dose cannot be fully gauged for at least 4 to 8 weeks when long-acting drugs (which are best), such as 'Marcoumar', are used or for as much as 3 to 5 weeks when shorter-acting drugs, such as phenindione, are used To change the dose, therefore, on results of blood-tests taken more frequently is to lead to inaccurate assessment of the dose and inadequate control

One of the most difficult problems, not emphasised enough, is the question of intercurrent illness The patient's anticoagulant requirements will then be sharply reduced, particularly if he is not taking his usual diet It is essential therefore to emphasise not only to his doctor but also to the patient the need for more frequent blood-tests during illnesses and the probable necessity for a reduction in the maintenance dose If oral antibiotics are given at the same time the risk of bleeding is materially increased All these details connected with treat-

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1 Rytand D A *Arch intern Med* 1951 88 207
2 Manson D I Fullerton H W *Brit med J* 1956 i 6
3 Bjerkeland C J *Acta med scand* 1957 suppl 330
4 Evans W *Proc R Soc Med* 1954 47 320
5 Wright H P Kubik M M *Brit med J* 1953 i 1021
6 Laurie W Woods J D *Lancet* Feb 1 1958 p 231

ment must be frequently repeated to the patient hence the value of his attending personally for his blood-test

You quote Manchester's[1] views on the limitations of the present oral anticoagulants subsequent infarctions occur in spite of anticoagulant therapy I have not had a single death from proved recurrent infarction, but patients have died of progressive cardiac failure Something more than long-term anticoagulant therapy is therefore needed to halt the progress of the disease Whether this can be achieved by diet remains to be proved I believe that, since a palatable diet can be constructed containing adequate unsaturated fats and a minimum of saturated fats, it is worth while prescribing such diets until more conclusive evidence is available

As you remark, no half-measures will be effective My experience for the past 4 years in organising an anticoagulant clinic has shown that effective long-term anticoagulant therapy can be given only in special clinics by doctors experienced in the use of such treatment. The treatment of a few patients by physicians who do not regularly use anticoagulant drugs will inevitably lead to serious mishap or, just as important, to inadequate control with no benefit to the patient.

New End Hospital,
London, N W 3
M TOOHEY

SIR,—I should be grateful if any of your readers could explain to me why the most restless, never stationary, constantly disturbed and perhaps most rapidly moving blood in the body—namely, that in the vessels and cavities of the heart—requires anticoagulant therapy to keep it from clotting in the treatment of coronary disease Indeed, if the clotting power of the blood causes or contributes to coronary occlusion, then in the same person at the same time there should be numerous clotting episodes elsewhere in the body where the blood is far less turbulent

It seems to me there is little doubt that coronary occlusion is due to occluding factors or to degenerative or inflammatory lesions in the coronary-artery walls, but considerable doubt that the clotting power of the blood plays any significant role The blood "fats" may play a greater part than we give them credit for

Port Elizabeth
W H CRAIB

CHLOROTHIAZIDE AND HYPOTENSIVE ACTION OF MECAMYLAMINE

SIR,—Although the observations of Dr Harington and Dr Kincaid-Smith (Feb 22) show that 1–1 5 g chlorothiazide reduces the urinary elimination of mecamylamine and that this action may be due to an increase in urinary pH, a number of quantitative and temporal considerations suggest that the potentiating effect of chlorothiazide in reducing blood-pressure may be related also to other factors

Milne et al[2] have shown that, in the first 24 hours following an oral dose of 10 mg mecamylamine, the mean total excretion in weakly acid urine is 37%, but it is only 13% when the urine is made alkaline with sodium bicarbonate or acetazolamide, to a pH above 7 5 Although Dr Harington and Dr Kincaid-Smith do not report urinary pH values in their paper, in our experience 1 g chlorothiazide seldom causes such a degree of alkalinity, and the action of mecamylamine may be potentiated with doses as small as 0 25 g of chlorothiazide

Quantitatively there appears to be a difference between the hypotensive effects of mecamylamine plus chlorothiazide and of mecamylamine plus acetazolamide the first combination is usually more potent, yet acetazolamide induces a more alkaline urine.

As Dr Harington and Dr Kincaid-Smith point out, the administration of chlorothiazide to a patient already taking mecamylamine may cause, after the first dose, a substantial fall in blood-pressure This potentiation may occur within 2–6 hours, at a time when, according to fig 1 in their paper, there is as yet no change in the rate of mecamylamine excretion It is this speed of action which also makes sodium depletion unlikely to be the sole factor in potentiating the hypotension

In time, no doubt, this action of chlorothiazide will be completely understood, but any explanation should take into account the potentiation of antihypertensive compounds other than mecamylamine We agree that by itself chlorothiazide has no hypotensive effect (except perhaps in pre-eclamptic toxæmia), but have found that as little as 0 25 g of chlorothiazide twice daily may reduce substantially the amount of mecamylamine needed to maintain a satisfactory lowering of blood-pressure and, most important of all, this may reduce to insignificant proportions the uncomfortable side-effects of the latter drug

London, S W 1
R I S BAYLISS
P R FLEMING
J R REES

SHADOW AND SUBSTANCE

SIR,—Dr Bickford's excellent article (Feb 22) on the increasing liberties and opportunities extended to his patients, and the results thereof, is encouraging and stimulating

I agree with him in deploring those who proffer as their sole evidence of progress the existence of an "open door", but equally to be criticised are those who dismiss the topic in scathing terms The open door is a misplaced term which has become a matter of heated controversy for some psychiatrists, and it is the Morton's Fork upon which more than one luckless candidate has been spiked at an appointments interview

Whether the ward door is permanently ajar or closed periodically as changing circumstances may dictate is surely of no importance as long as the *concept* of the open door remains within the mind of the patient and his doctors The open door itself may well be the symbol to a chronically deprived patient that the world is not shut off from him, but the "open door" *concept* of increased opportunities for rehabilitation toward a normal society is what really matters, as Dr Bickford has illustrated

To those who advance the open-door system as their contribution to progress I would refer pp 376–378 of Tuke's *History of the Insane* Too long to quote in full, the chapter entitled The Open Door System includes

> "It is only of late years that the disuse of locked doors has been regarded as an important feature in administration
>
> " it became in the interests of the attendant to engage the patient in such occupations as would make them contented, to provide an outlet for their energies, and to direct their minds from thoughts of escape The relations of an attendant to his patient thus assumed less of the character of a gaoler and more that of a companion or nurse and it was eventually found that this change in character of the form of control could be adopted in the treatment of a much larger number of patients than was at first anticipated

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1 Manchester B *Ann intern Med* 1957 47, 1202

2 Milne M D Rowe G G, Somers K., Muehrcke, R C., Crawford, M A. *Clin Sci* 1957, 16 599

> "The number who form a definite purpose to escape really constitutes only a very small proportion.
>
> "The special watchfulness required of the attendants in guarding against escape need be directed to only a few.
>
> "It appeared further that the disuse of locked doors had an influence on some of the patients in diminishing the desire to escape.
>
> "It is year by year becoming more clearly realised that many advantages result from the working of the open door system and *it has now been adopted to a greater or lesser extent in most of the Scotch asylums.*"

Progress in 1958? This report was published in 1881.

London, W 1 J Stuart Whiteley

SERUM-POTASSIUM LEVEL IN RESPIRATORY FAILURE

Sir,—The observations by Dr Foulds and her colleagues (Feb 22) on hyperkalæmia in respiratory acidosis are of considerable interest. Over the past eight years we have studied at least 150 patients with respiratory failure and confirm that moderate hyperkalæmia is not uncommon—especially in severely anoxic patients and in those who are moribund. We have not, however, seen serum-potassium values higher than 7·0 mEq per litre, even in patients who have died within a few minutes of the blood sample being taken. The accompanying table gives details of some of the cases that we have studied. Blood was collected without hæmolysis, and in most cases serum was separated within thirty minutes.

We should not regard an isolated serum-potassium of less than 7 mEq per litre as having much clinical significance. Studies in acute renal failure [1, 2] indicate that cardiac arrest is unusual until the serum-potassium rises above 8–9 mEq per litre.

We have been more impressed by the importance of *hypo*kalæmia in respiratory failure—especially in patients treated with mercurial diuretics, acetazolamide, steroids, or chlorothiazide. We believe that, in cor pulmonale, respiratory failure may be potentiated or maintained by potassium deficiency. These observations will be published soon.

Middlesex Hospital, London, W 1 E Keith Westlake

Chase Farm Hospital,
Enfield, Middlesex. Thomas Simpson

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[1] Swann, R C, Merrill, J P *Medicine*, 1953, 32, 215.

[2] Evans, B M, Hughes Jones, M C, Milne, M D, Yellowlees, H *Lancet*, 1953, ii, 791.

SERUM-POTASSIUM LEVELS IN RESPIRATORY FAILURE

Case	Age	Sex	Oxygen tent or air	Date	Arterial oxygen saturation (%)	pH	Plasma-CO$_2$ content (mEq per litre)	pCO$_2$ (mm Hg)	Serum potassium (mEq per litre)	Serum sodium (mEq per litre)	Blood-urea (mg per 100 ml)	Heart failure	Mersalyl	Progress
1	67	M	A	Jan 28, 1953	—	6·81	—	—	6·4	—	—	+	+	Died 15 min later
2	76	M	A	Dec 18	81·4	7·34	29·3	51·7	—	—	—	+		Died Dec 24
			O	Dec 19	100·0	7·28	32·9	66·3	4·3	140	—	+		
3	52	M	A	Jan 5, 1954	53·4	7·33	36·2	65·7	—	—	—	+		Recovered
			O	Jan 6	97·5	7·07	39·4	102·3	5·5	138	33	+	+	
			A	Jan 30	88·8	7·40	27·8	43·4	—	—	—	0		
4	60	M	O	Jan 8	—	7·03	17·7	61·0	5·0	145	57	0		Died from combined metabolic and respiratory acidæmia 11 hr later
5	67	F	A	Feb 2	38·4	7·25	34·3	73·7	6·3	137	132	+		Died 4 hr later
6	62	M	A	Feb 2	64·0	7·26	33·6	71·6	5·1	140	39	+		Died 9½ hr later
			O	Feb 3	100·0	7·26	44·0	97·0	4·6	138	—	+	+	
			O	Feb 4	100·0	7·33	48·2	110·0	4·9	—	—	+		
			O	Feb 6	100·0	7·32	52·0	115·0	3·8	132	—	0		
			O	Feb 7	100·0	7·32	50·6	111·0	4·0	—	—	0	+	
			A	Feb 7	72·6	7·41	48·7	74·6	3·6	130	—	0		
			O	Feb 8	94·0	7·12	42·6	121·0	6·2	135	—	0		
7	67	M	A	Feb 25	57·5	7·32	36·0	66·5	4·1	150	68	+		Died March 3
			A	Mar 2	—	7·19	32·7	74·5	5·7	140	208	0		
8	71	F	A	Dec 10	56·8	7·30	34·4	67·1	—	—	—	0		Recovered
			A	Dec 14	—	—	40·3	—	3·3	—	35	0		
9	65	M	A	Dec 16	83·0	7·42	32·7	48·6	—	—	—	+		On corticotrophin and KCl, recovered
			A	Dec 18	—	—	—	—	2·0	138	31	+	+	
			A	Dec 21	—	—	31·8	—	4·8	134	54	0		
			A	Jan 7, 1955	—	7·38	25·3	42·9	—	—	—	0		
10	65	M	A	Jan 13	79·0	7·36	26·9	16·0	—	—	—	+		Died 12 hr later from massive hæmatemesis from duodenal ulcer
			A	Jan 15	—	—	—	—	7·0	131	—	+		
11	49	M	A	Mar 1	30·0	7·25	36·0	78·0	—	—	—	+		Died March 9
			A	Mar 2	—	—	—	—	5·9	126	132	+		
			O	Mar 6	63·0	7·05	42·0	133·0	—	—	—	+		
12	18	M	A	Jan 3, 1956	—	7·29	41·0	82·0	4·5	142	23	0	—	Recovered
			A	Jan 21	—	7·39	35·0	55·0	—	—	—			

EARLY ADMISSION TO HOSPITAL OF MENTALLY DEFECTIVE BABIES

Sir,—The writers of the interesting letters on home and institutional care of mongols might like to have figures from a private midwifery unit.

3000 babies were born in a period of twelve years, of these 7 were mongols, and 2 stillborn infants had strongly mongoloid features. Of the 7 surviving infants, 4 went to their own homes, 3 are alive and thriving, but in one case the mother has developed a neurosis which, one suspects, began because she had given birth to a mentally defective child, she was 39 and at the age of 25 she had had a healthy illegitimate child adopted.

2 children went to residential nurseries, of these 1 died at 6 months from pneumonia, and the other at 10 months from measles and bronchitis. The third one, an illegitimate child of a woman aged 42, went to a foster-mother and later to hospital, where she died. The diagnosis was congenital heart-disease and pneumonia.

Having observed many families over several years, I do feel they should be given much individual and unhurried advice. There is no doubt that the presence of an older mentally defective patient can put an intolerable strain on a family From my own experience I would agree that the mother and father of a newborn infant should not be told the worst at the onset It should be a gradual process Great consideration should be given to their own mental make-up and, in the case of those who obviously could not take the burden, the decision should be taken for them by a doctor whom they can trust

Lancashire MATRON OF MATERNITY HOME

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—In Mr Moloney's paper (Feb 8), and in the subsequent correspondence, no comment has been made on the most serious indictment of nylon used anywhere in the body

Harrison and Adler [1] have shown that six months after the insertion of nylon into the tissues 80% of its tensile strength is lost—figures which we can confirm from studies made in this department These workers, however, found that nylon did not seem to degenerate further when left implanted for longer periods Such loss of strength is almost certainly due to chemical degradation which is to be expected from its chemical structure

The residuum of tensile strength after six months in the body may well enable nylon to maintain the repair of a hernia, but, to use Mr Moloney's simile, an engineer would surely be distressed to find the reinforcing bars of his concrete so weakened after so short a time

'Terylene' ('Dacron') and Courtauld's 'Courlene X3' polyethylene do not so weaken, and may eventually prove to be more satisfactory than nylon

University Department of Surgery,
The Royal Infirmary,
Sheffield B N CATCHPOLE

SIR,—It is significant that letters on the use of buried nylon should immediately follow those on septic surgery (Feb 22), for, in fact, the two problems are really one

No matter how well constructed the theatre and how careful the technique, perfect asepsis is impossible, and there is *always* some air infection which may alight on sutures before they are inserted

I have for some time held the view that the failure of the multifilamentous or braided suture is caused by the individual strands of nonabsorbable material being so close together that the defence mechanisms cannot reach airborne infection lying between the strands, so that it can develop to the stage where wound infection becomes obvious

With the monofilamentous material, on the other hand, the organisms are not protected from the natural defence mechanism, and wounds heal cleanly With our present standards of asepsis, we must accept it as a fact that *every* surgical wound is infected and that whether nonabsorbable sutures are used or not, it is only the patient's resistance which allows healing by first intention

Having had the same experience as your other correspondents with multifilamentous sutures, I have used only monofilamentous nylon for over ten years for abdominal wounds as well as herniæ I found, however, that, particularly in the abdominal wounds fine nylon (no 5) occasionally snapped when the patient coughed during convalescence This problem has been solved by using stainless steel for all the deep repair of herniæ, and reserving nylon for the aponeurosis where the stress is less As regards method, my personal preference is for the McVey repair

No surgeon can claim that every hernia heals by first intention, but no monofilamentous suture material has had to be removed for more than five years in my cases

Rochdale A M MCMASTER

SIR,—The nylon used in the 17 men who developed a chronic sinus after an inguinal hernia repair (described in my letter of Feb 15) was mostly monofilamentous, no 8 being the size used most often In the particular series reported, there were 550 other cases where nylon was not the principal suture material Only 5 of these developed sinuses—and 3 of these had had a McArthur repair where the fascial strip had been secured with nylon, 2 of these did not heal until a nylon knot had been removed

I find it impossible, therefore, to agree with Mr Haxton (Feb 22) that "in the presence of sepsis wound healing progresses rapidly and without extrusion of the sutures" (where nylon has been used as the suture material) Nor can I agree that "monofilamentous nylon gives less trouble from infection than the other suture materials in common use" Mr Seth-Smith's experience (Feb 22) is far more usual than Mr Haxton's I do not doubt the value of nylon as a suture material, but in making his choice of the most suitable material for a particular case, a surgeon should be fully aware of the serious disability which often follows the supervention of sepsis where a non-absorbable foreign suture material has been used

St Helens,
Lancs A J MARSDEN

PREMEDICATION FOR GASTROSCOPY

SIR,—I was much interested to read the letter from Mr Miln (Feb 15) in which he describes the advantages of chlorpromazine over morphine in the premedication of a patient having gastroscopy

I gave up using morphine as a premedication for gastroscopy several years ago The majority of my gastroscopy patients are examined as outpatients, and it is inconvenient to use a substance such as morphine which may have prolonged undesirable effects This occurred to me most forcibly when I had it myself in the role of a "guineapig" for one of my colleagues who was studying pain and analgesia Although perfectly well when lying down, I was giddy for several hours when standing up I have also observed nausea and vomiting in normal subjects to whom I have given morphine for experimental purposes The chief use of morphine should be to mitigate severe pain For gastroscopy the main need is to allay anxiety I have found that amylobarbitone sodium gr 3 by mouth, given 45 minutes before the examination, is sufficient for this purpose If the patient is very large or unduly apprehensive the dose can be doubled

As well as the barbiturate, atropine gr $^{1}/_{100}$ is given by injection 45 minutes before the procedure Atropine, or some similar substance, is essential Without it, the secretion of mucus is heavy and may obscure the view in the stomach Brisk salivation during the procedure may embarrass respiration I found this when I omitted atropine deliberately when studying fibrinolysis in relation to anxiety and wished to see the effect of gastroscopy undisturbed by the pharmacological actions of atropine

I agree that sucking a lozenge containing an appropriate anæsthetic is sufficient to anæsthetise the throat, though I like to use in addition a gargle of 1% amethocaine as advocated by Dr Avery Jones

Some gastroscopists are in the habit of washing the stomach out before the procedure This is quite unnecessary in the majority of patients What I do myself is to tell the patient to eat no solid food but to have one or two cups of tea on the morning of the examination The stomach is then washed through in a way agreeable to the subject The only exception is if the barium-meal examination, which must precede any gastroscopy, has shown evidence of pyloric stenosis with retention of gastric contents

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[1] Harrison, J H, Adler, R H *Surg Gynec Obstet* 1956, 103, 613

Nuffield Department of Clinical Medicine,
Radcliffe Infirmary, Oxford

S C TRUELOVE

LEG SUPPORT FOR USE DURING VAGINAL OPERATIONS

SIR,—I have noted with interest the description of leg supports by Mr T B FitzGerald[1] They seem, however, to have some disadvantages

Extreme abduction of the thighs, as shown in the photograph, is accompanied by pronounced lordosis of the lumbar spine, and this, in turn, is followed by postoperative backache[2] The popliteal vessels are compressed by the proximal free edge of the canvas support

Moreover, it seems from the illustration and the description that the assistants do not have free access to the field of operation

For several years I have used a modification (see accompanying figures) of the leg support described by Waddell,[3] which has the following features to recommend it

(1) The feet are supported by a simple half-boot made of 3 inch-wide canvas webbing, with a sponge-rubber pillow behind the tendo achillis (fig 1)

(2) The thighs are not abnormally abducted, and adjustment can easily be made for flexion and extension of the knees and abduction and adduction of the thighs (figs 2 and 3)

(3) There is no pressure on the leg or thigh at any point

(4) The feet can be placed in the boot with great ease

(5) The assistants have unobstructed access to the field of operation All can be seated if desired

(6) Backache due to the lithotomy position is not a complication when this apparatus is properly used

Manitoba Clinic
Winnipeg, Manitoba

A M GOODWIN

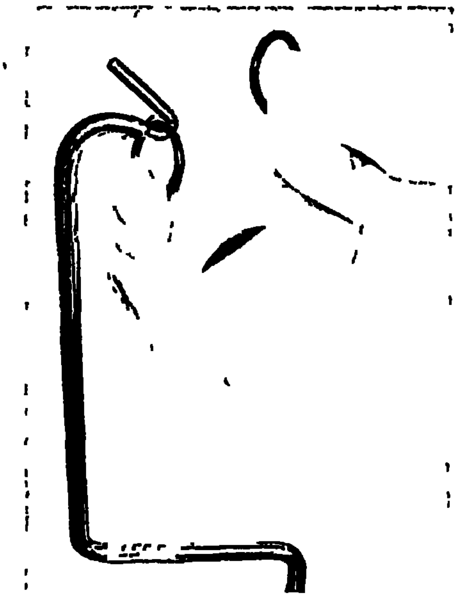

Fig 1

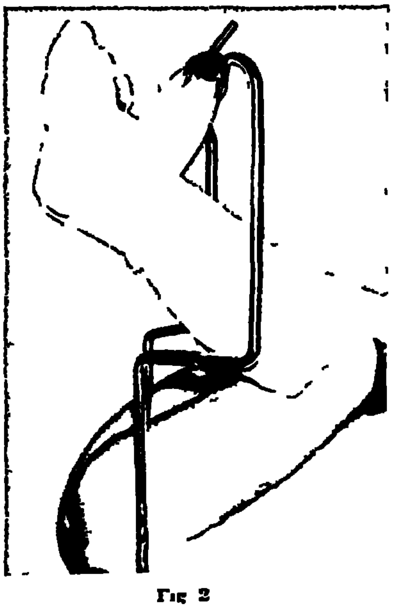

Fig 2

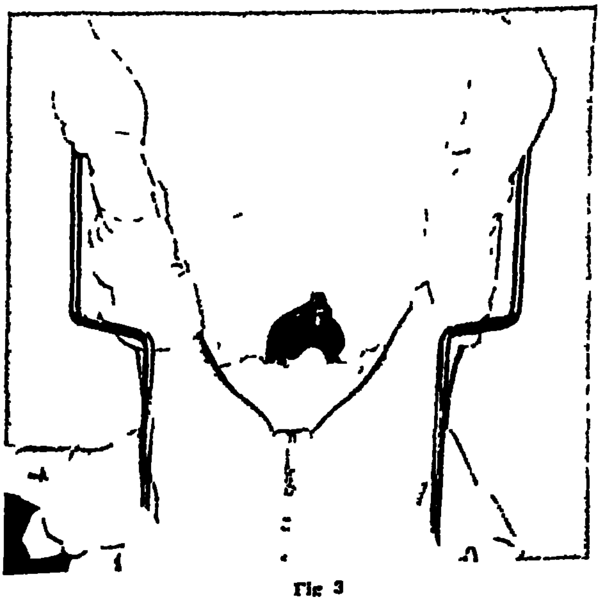

Fig 3

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[1] Lancet, 1957, ii, 577

[2] Hunter, R G, Henry, G W, Larsen, J J *Obstet Gynec* 1954, 4, 344

[3] Waddell, W R *Amer J Obstet Gynec* 1949, 58, 818

SPINAL ANÆSTHESIA

SIR,—Mr Lake's plea (Feb 22) for a new interest in spinal anæsthesia is thought-provoking and persuasive Nevertheless, I strongly support the conclusion of your annotation that the hazard of permanent damage to the nervous system is a serious one In my practice as an orthopædic surgeon, spinal anæsthesia was frequently used in the past I never had any serious complications such as paraplegia There was one case of persistent incomplete paralysis and headache Other surgeons in the area were not so fortunate and a few years ago it was a well-known fact that one solicitor, a man of high principles and of an excellent reputation, was so convinced of the dangers of this method of anæsthesia that the litigation he instituted might almost be said to constitute a vendetta

I cannot help feeling that Mr Lake has omitted in his list of risks a very important hazard—namely, damage to an intervertebral disc Quite apart from the question of spinal anæsthesia many cases of infection of intervertebral discs have been recorded in the past ten to fifteen years as a result of lumbar punctures which one must presume were inexpertly carried out These cases prove that the intervertebral discs can be infected by the lumbar-puncture needle In the course of obtaining the history of many hundreds of patients suffering from backache, lumbago, and sciatica it was forced on my consciousness that an extremely high number related the onset of their symptoms to an operation performed under spinal anæsthesia Very occasionally, the onset was related to an operation performed under general anæsthesia and this must be mentioned even though it appears to destroy the force of my argument However, some of these operations involved the lithotomy position Since the number of operations performed under spinal anæsthesia has dropped this history has not been obtained It was these cases, more than anything else, which caused me to prohibit the use of spinal anæsthetics for my patients

Manchester W SAYLE-CREER

INFANTILE GASTROENTERITIS

SIR,—Dr Librach (Feb 22) has made it abundantly plain that he does not believe in the pathogenicity of serotypes of *Escherichia coli* in infantile enteritis *Hæmophilus influenzæ*, he says, was once held to be the cause of influenza, now known to be a virus disease, therefore the laboratory has misled and hindered the clinician He then implies that the laboratory work on the serology of *Esch coli* has done a similar disservice to medicine by confusing rather than explaining the ætiology of infective enteritis in infants

He does not disclose his reasons for doubting all the work which has been published on the subject during the past 10 years He has quoted a passage from a paper [1] of which I was one of the authors Lifted out of its context this quotation would suggest that the authors themselves doubted the significance of finding *Esch coli* type O 111 in infantile enteritis This is not the case, the quoted passage does not represent the thesis of the paper in question, nor does it reflect the views of its authors at the time when it was written, much less so now

City General Hospital,
Stoke-on-Trent C GILES

SUDDEN DEAFNESS

SIR,—Mr Boyes Korkis (Feb 22) rightly stresses the need for treating patients with sudden perceptive deafness "as an absolute emergency" He goes on to say that "a therapeutic trial of a stellate block would yield useful information and if carried out early enough would have a greater chance of success" I can assure Mr Korkis it not only *would* but *does*

Like Mr Korkis, I do not advocate the use of intravenous nicotinic acid because I cannot see the advantage of this over a stellate block Audiograms should be done immediately before the block and half an hour after under good conditions by a skilled technician in every case, and an efficient vasodilator drug—I use buphenine ('Perdilatal')—plays (not "could play") an important part in maintaining the good effect of a successful stellate block

Mr Korkis goes on to say that the old expectant attitude in sudden deafness of this type must change to one of action I agree, but it must change similarly in the treatment of Ménière's disease [2] Having done about 600 stellate blocks for inner-ear disorders during the past five years, under ideal audiometric conditions, having produced on many occasions a significant rise in hearing by stellate block, and having demonstrated by visual observation and lately by nystagmography the complete return of vestibular function after sympathectomy, I am convinced that many cases of sudden deafness of perceptive type—especially in young patients—have an ætiology essentially similar to that of Ménière's disease, and that the new approach to these disorders, first demonstrated by Mr E Garnett Passe, has gone for too long without recognition

Tyrone County Hospital T J WILMOT

CLINICAL GERIATRICS

SIR,—May I thank and commend you for your annotation on this topic last week? The special problems associated with the care of elderly patients are not known as well as they might be The present medical curriculum gives students little teaching and less experience in this branch of medicine In consequence, when they go into practice, they find themselves confronted with unfamiliar situations for which they have not been prepared by their teachers Is it not time to press for more clinical instruction in geriatrics? Surely the changes in our population make the care of elderly patients one of the most important tasks confronting our profession in this day and age

London, S W 16 TREVOR H HOWELL

SOFT-TISSUE RADIOGRAPHY IN ESTIMATING FŒTAL MATURITY AND POSTMATURITY

SIR,—Your leading article of Feb 1 is really encouraging Every experienced obstetrician knows the difficulties and fallacies in the evaluation of the advancement of pregnancy These difficulties in the diagnosis of fœtal maturity are sometimes even greater with overmaturity, a problem which was repeatedly discussed in recent issues of your journal [1–3] although from the therapeutic point of view only The diagnosis of prolonged pregnancy is certainly as great a problem as its therapy

Hartley's critical analysis of the value of the appearance of epiphyseal calcifications for the diagnosis of the duration of pregnancy and the good results achieved by him in Manchester are reassuring I should like to add one sign which for the past ten years has been very helpful in assessing fœtal maturity and overmaturity in our X-ray diagnosis laboratory

Fat tissue is accumulated only in the last weeks of fœtal life and the subcutaneous tissue of premature fœtus or newborn is almost devoid of fat coat On X-ray pictures of premature pregnancies the subcutaneous fat-tissue shadow is usually easily discernible especially on the buttocks, the knees, and the elbows as a distinct subcutaneous shadow line of 1–3 mm thickness The presence of this sign allows for the diagnosis of a full-term fœtus, with the one exception of a diabetic pregnancy where a giant fœtus might show this symptom much earlier (where, anyhow, it might add to the indications of an earlier termination of pregnancy)

In a prolonged pregnancy in which there is a deteriorating caloric supply through the degenerating, senescent placenta the fœtus has to use up its own energy stocks—in the first place, its subcutaneous fat tissue The disappearance of the subcutaneous fat-tissue shadow, especially if it was easily visible on a previous X-ray picture a week or two before, speaks for the diagnosis of a biologically prolonged pregnancy and for the necessity of a prompt termination of pregnancy, because of danger of anoxia and fœtal distress

If there has been no previous X-ray, as often happens, a large fœtus with a fully developed and well-calcified skeleton but without a visible subcutaneous fat-tissue shadow is always suspect for overmaturity A high standard of radiographic technique is essential This sign must always be evaluated in conjunction with other clinical, radiological, and laboratory signs, never separately It is especially helpful in positive cases for the exclusion of prematurity or overmaturity, less reliable in negative cases where it might sometimes be not recognisable, owing to faulty technique or lack of experience

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[1] Giles, C, Sangster, G *J Hyg, Camb* 1948 46, 1

[2] Wilmot T J *Brit med J* 1957 ii 1047

[1] Gibberd G F *Lancet*, Jan 11 1958, p 64

[2] Parker, R B *ibid* Feb 1, p 265

[3] Wa sen, P S *ibid*

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JÓSEF BIENIARZ*
ALINA ŚMIGIELSKA

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

SIR,—In discussing the increased frequency of toxæmia of pregnancy and pre-eclampsia in patients with beriberi and in areas where pellagra is endemic, Professor Browne (Jan 18) ascribes this phenomenon to lack of vitamin B

It may be of interest to draw attention to the relationship between some vitamins of the B complex and the adrenal glands In patients with beriberi, often characterised by a general dropsy, the adrenals are hyperplastic [1] when these patients take vitamin B_1 (aneurine) the hyperplasia disappears

The relation between pellagra-preventing factor (P P factor) and the adrenals is under discussion, some authorities suggesting that lack of the P P factor causes atrophy of the adrenals But the P P factor alone cannot cause disappearance of all the symptoms of pellagra, to this end tryptophan and riboflavine must also be given The adrenals play an important part in the synthesis of riboflavine by making possible the conjugation of the components of riboflavine with phosphoric acid

It is highly probable that the increased frequency of toxæmia of pregnancy and pre-eclampsia in patients with beriberi and pellagra must be ascribed to the adrenals too

Amsterdam, Holland

R SCHUURMANS

ON TAKING THE TEMPERATURE IN THE MOUTH AND THE AXILLA

SIR,—Dr Loudon's interesting observations [2] on the oral and the axillary temperatures prompt me to describe my experience in recording the body temperature So far one hundred and thirty healthy people in different age-groups have been examined Details of a bigger series are expected to be published elsewhere

One standard half-minute thermometer—a locally popular brand of English make—was used throughout the period of observation In every case the mercury column was shaken down to 95 F and the instrument placed under the tongue or in the axilla It was taken out, read, and replaced gently every half-minute till two consecutive readings were identical The first of the last two readings was recorded as the time required for attaining maximum temperature It varied between 3 and 5 minutes for the axillary and $1^1/_2$ and 2 minutes for the oral temperature

While Dr Loudon's emphasis on various factors influencing the axillary temperature is justified, I might add that a little friction with dry linen to wipe off sweat from the axilla, whether there be any or not—as is common practice here—may considerably increase the recorded temperature, specially in children In one case the increase was as much as 1 F

I was, however, more interested in the problem of recording the body temperature of unconscious patients In unconscious patients the thermometer cannot be safely and properly introduced under the tongue Therefore, an alternative method of recording the oral temperature could be helpful if it is reasonably accurate

With that idea in view the thermometer was introduced in the groove between the cheek and the gum as far as it could go and the temperature recorded in the usual way This was successfully and easily done in several unconscious patients The time required to record maximum temperature was the same as under the tongue

The relationship between the temperatures recorded was

			No of patients
Under the tongue	<	in the cheek	26
Under the tongue	=	in the cheek	16
Under the tongue	>	in the cheek	88

Generally, therefore, the temperature in the cheek tends to be lower than the temperature under the tongue, but there is a wide range of variation

Difference	*No of patients* *tongue > cheek*	*cheek > tongue*
0 2°	24	7
0 4°	22	11
0 6°	18	4
0 8°	13	3
1°+	11	1
	88	26

Thus, the temperature recorded in the cheek is not a good substitute for the temperature recorded under the tongue, but can serve as an alternative if necessary, provided allowance is made for possible differences

Department of Medicine,
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Calcutta, 14

S N SENGUPTA

BED REST, THROMBOSIS, AND EMBOLISM

SIR,—In your comparison last week between modern surgeons and their cavedwelling ancestors, you accuse the lot of fetishism in their postoperative incantations But, Sir, you omit to mention the small matter of the Atom Age and Stone Age patient One may imagine the long struggle to get the latter to the stone table, to keep him down—unless hit on the head—during the operation, and finally the patient's sprint, beating ten seconds, to leave the painful scene Such problems then as breathing and moving did not arise for the palæolithic surgeon! With his physiology equally up to date, the modern surgeon has his difficulties, as it were, in reverse, in an issue between, say, a demand for calm—even in the absence of cameras—and the risk of clotting!

London, W 1

F D SANER

VALIDITY OF THE UREA METHOD FOR ESTIMATING TOTAL BODY-WATER IN MALNUTRITION

SIR,—Dr FitzGerald (Jan 11) rightly points out the possibility of incomplete absorption of urea, when given in large doses (of the order of 100 g a day) We have used only 20 g in our studies for the estimation of total body-water Even at this low level the possibility of incomplete absorption of the urea administered was considered by us, especially in view of the altered condition of the gastro-intestinal tract in patients with nutritional œdema Total body-water was estimated in two normal subjects and in two patients with nutritional œdema, at different levels of urea administration—10 g and 20 g The values obtained agreed very closely, both in the normals and in the patients, indicating that, at the low levels of 10 g and 20 g of urea, the absorption is probably complete

It is possible, as Dr FitzGerald has pointed out, that urea may be broken down into ammonia by the gastric urease, and its distribution in the various fluid compartments may not be strictly uniform, but the fact that the values obtained by the simultaneous use of antipyrin and urea were nearly similar would indicate that these factors are not of such magnitude as to interfere with the estimation

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* Present address Department of Anatomy, College of Medicine, University of Illinois, 1853, West Polk Street, Chicago 12, Illinois

[1] Abderhalden E Lehrbuch Physiologische Chemie, pp 251, 253 Basle

[2] Loudon, I S L *Lancet*, 1957, ii, 233

Nutrition Research Laboratories
Coonoor, S India

S G SRIKANTIA
C GOPALAN

THE LIFE FOR ME

SIR,—Dr Scott (Feb 15) rightly criticises me for not plugging preventive psychiatry (though in all fairness I did give it a passing mention) It isn't easy to cover one's whole specialty in two and a half brisk columns

It is good news that he and some psychiatrists are cooperating in preventive work, and I look forward indeed to hearing more about it He mentions clinics, though I have an awful feeling that he is only referring to child-guidance work, these weren't the ones I was referring to in the Widdicombe File I was harking back to the infant-welfare and toddlers and all that, whereas the good G P is well-enough qualified to take these over, I rather doubt if many would be happy as child psychiatrists, let alone set aside a corner of their surgeries for the usual clinic accretion of sand, water, and shattered toys But if Dr Scott thinks child-guidance clinics are preventive I must disagree the ones I worked in were dealing only with disturbed children, to say that they are preventive *because* treatment early means less delinquency and neurosis is much the same to me as saying that major surgery is preventive because you hope to prevent the patient's death The only approach to real preventive psychiatry that I have yet heard of appears in what I believe are the terms of reference of the Ingleby Committee—namely, to consider whether local authorities should have new powers to prevent or forestall the sufferings, mental and physical, of children in their own homes I must say I hope they get them

Far from being antipathetic towards child guidance, may I assure Dr Scott that I wouldn't mind going in for it myself Perhaps I may interject, though, that these S H M O vacancies don't interest me much it will be consultancy or nothing, and I'm afraid the same goes for my pals

Widdicombe-in-the-Moor RICHARD COBBLEIGH

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—As I read Dr Ryle's letter last week, I surmised that Dr Ryle must be a competent well-qualified young man with several hospital jobs to his credit, but with less than ten years' experience of general practice My surmise was confirmed by reference to *The Medical Directory* Even Dr Ryle, who feels he can write more easily than others about scientific detachment, is writing within a circumscribed pattern that can be discerned by his less scientific colleagues

Dr Ryle feels that the personality of the doctor is receiving too much attention in the description and investigation of disease, and that "facts, based on observation and experience, can guide our actions irrespective of our personalities " The trouble is that if we practitioners do not take our personalities into account, we pick up the wrong facts and come to the wrong conclusions, and we ignore the reality of functional or stress disorders which form such a large part of our work

When, for example, we investigate a case of dyspepsia by a scientific inquiry related to the function of the stomach, and find no abnormality, we make a diagnosis of functional disorder and reassure the patient there is nothing really wrong as no organic disease can be found We get a little ruffled when the patient turns up a few weeks later asking for more X-rays as his symptoms have continued unabated in spite of our reassurance, and it is only when we can make a personality change, by realising that we have been reassuring ourselves and not the patient, that we can take further steps to help the patient What a small, and yet what a vast, change takes place when we stop asking our patients detailed questions about their functional disorders and attempt to listen to the expression of their real feelings and fears! In such cases we lay aside the tools of scientific inquiry that are used for the investigation of organic disease, and pick up the tools that help us to interpret the language of functional disorder—a language that has still to be learnt by the medical profession

Dr Ryle writes of the need for scientific detachment This is easier for the hospital doctor to achieve, as so many hospital patients learn to their cost Perhaps the main difference between hospital and general practice is this very matter of detachment, the too-objective approach in hospital and the too-subjective approach in general practice The validity of Dr Clyne's article of Feb 1 cannot be in doubt The masterly way in which Dr Clyne gave verbal expression to his attitude towards his patient made me feel that here at last was an attempt to describe the very stuff of general practice

London, W 8 H STEPHEN PASMORE

A PLASTIC APPROACH TO SURGERY

SIR,—If a scientific communication is to be understood universally it is essential that terms should be used with accuracy and precision When Mr Heanley uses the term Langer's lines he can scarcely object if a reader assumes that he means the lines described by Langer From the definition which he now gives (Feb 22) it appears that this is not so Unfortunately his definition is not of a Langer's line but rather of what he might have called with more accuracy a " line of election for surgical incision " As I pointed out (Jan 25) the two terms are not synonymous

On the question of priority of description Wood Jones[1] makes some interesting observations which are also at variance with Mr Heanley's statements

Glasgow Royal Infirmary IAN A McGREGOR

RADIOSTRONTIUM IN BONES

SIR,—The following observations are based on reading your informative annotations and articles during the past year, and some of the publications which you have reviewed

Some indication of the possible world-wide increase in the distribution of strontium 90 is given by the following figures quoted from an A E R E report[2]

Concentration on ground on Jan 1, 1956	4 5 mc per sq km
Maximum concentration on ground due to bombs exploded by that date (this will be reached in about 1969)	14 mc per sq km
Equilibrium value (reached in about 100 years' time) if the present rate of weapon firing continues indefinitely	200 mc per sq km

Bryant et al[3] show clearly the routes by which strontium 90 is already entering the human body (e g, rain, soil, grass and other crops, cow's milk) and they say

"The highest ^{90}Sr activity in human bone found in our series to the end of 1956 is 1 55 S U which is 1/60 of the maximum permissible for the general population, and 1/6 of the level above which 'immediate consideration would be required'"

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[1] Wood Jones, F The Principles of Anatomy as Seen in the Hand, p 102 et seq London 1944

[2] Stewart N G, Crooks R N Fisher E M R The Radiological Dose to Persons in the U K due to Debris from Nuclear Test Explosions prior to January 1956 A E R E HP/R 2017 H M Stationery Office

[3] Bryant F J Chamberlain A C, Morgan A, Spicer G S Radiostrontium in Soil Grass Milk and Bone in the United Kingdom A E R E HP/R 2353 H M Stationery Office See *Lancet*, 1957, ii, 942

A conclusion which appears clear from these figures is that the strontium-90 content of children's bones will increase during the next ten years, even if there are no more test explosions With regard to the future, if similar explosions are continued, the figures quoted above appear to be the "writing on the wall" which could not be much clearer

London, S W 1 **Roy C Hoather**

INTRATHECAL PHENOL FOR INTRACTABLE PAIN

Sir,—Following the paper by Dr Nathan and Dr Scott (Jan 11), I should like to call attention to my letter in your columns last year [1] I pointed out that a watery solution of phenol injected into the perineural tissue through the first or second sacral foramen is highly efficacious in all forms of sciatica and in intractable pain, and does not cause any undesirable side-effects

I think this is a simple and safe method and does not necessitate the use of 'Myodil', silver nitrate, or the intrathecal application of phenol

St Istvan Hospital,
Budapest **T Lehoczky**

4-4'-DIAMIDINODIPHENYLAMINE IN MYELOMATOSIS

Sir,—I should like to draw attention to the encouraging results which have been obtained in the treatment of myelomatosis with 4-4'-diamidinodiphenylamine dihydrochloride (M & B 938)

This drug has previously been used in bronchopulmonary aspergillosis,[2] and it is chemically related to pentamidine and hydroxystilbamidine, which have been used in myelomatosis with only symptomatic improvement [3] [4] Because of this chemical relationship I decided to try its effect on myelomatosis

A man aged 36 was admitted to Charing Cross Hospital in August, 1953, with a history of pain in the right buttock for two years A cavity in the sacrum was curetted at operation, and biopsy showed plasma-cell myeloma A short course of radiotherapy was then given to the sacral area Radiographs showed two sharply defined osteolytic lesions in the skull so it was decided to give 4-4'-diamidinodiphenylamine Daily intravenous injections were given and the total dose was 1 2 g in a fortnight

The patient remained well until July, 1954, when he had sudden pain in the chest Radiographs showed osteolytic lesions in the ribs By January, 1955, his condition was worse and the erythrocyte-sedimentation rate was 70 mm in one hour (Westergren) Another course of the drug was given but on this occasion a total dosage of 1 7 g was spread over five weeks By the end of the course the patient was completely free of pain When last seen in October, 1957, the patient was perfectly well, the E S R had fallen to 22 mm in one hour and there was recalcification of the skull lesions

Myelomatosis is invariably fatal and the untreated disease advances steadily It is generally agreed that although pentamidine and hydroxystilbamidine sometimes relieve bone pain, the progress of the disease is unaffected Recalcification may follow radiotherapy and has been reported after treatment with urethane [5] Spontaneous recalcification must be rare, and according to Boyd it never occurs [6]

Although the above results were obtained in a single case and cannot carry much weight, they do suggest that the drug is worthy of trial in myelomatosis A dose of 0 1 g intravenously twice weekly is well tolerated and experience suggests that this should be continued to a total dosage of 2 g

Edinburgh **H W C Ward**

THE DIFFICULT KNEE

Sir,—In your annotation [7] you discuss the errors of diagnosis revealed at meniscectomy, and comment that the problems of meniscectomy are wider than one recent series suggests

Neither Murdoch nor you, however, mention the risk of failing to diagnose rheumatoid arthritis when it presents as internal derangement of the knee-joint It seems likely that this omission can be largely attributed to

(1) Inadequate follow-up of meniscectomy patients in general

(2) Continuing lack of awareness that rheumatoid arthritis quite commonly begins as a monarticular arthritis

(3) Failure to appreciate that rheumatoid arthritis itself can produce internal derangement

Patients who develop recurrent knee-joint effusion following trauma, and who give a history of locking and instability that is not quite typical of a torn internal cartilage, are often diagnosed as "cartilages" and not infrequently subjected to meniscectomy Both operated and unoperated patients with this diagnosis present themselves here with rheumatoid arthritis that is quite definite by the American Rheumatism Association criteria, and this may well be the experience of physicians in charge of rheumatic clinics in other parts of the world War pensioners who are necessarily subjected to follow-up examination for a prolonged period form a fruitful source of case material and sometimes bear bilateral meniscectomy scars before their rheumatoid arthritis involves a sufficient number of joints to become embarrassingly obvious One does not doubt that some of these patients did indeed have torn cartilages, but the significance of such lesions in the production of their symptoms is another matter

It is well known that nipping of hypertrophied rheumatoid synovial fringes can cause internal derangement of the knee-joint, the implication being that this occurs with such gross involvement that it would not easily be missed There is, however, a tendency, in less florid cases, for firm and fibrous synovial tags to form in a remarkably constant position, just deep to the inferolateral border of the patella Although these are usually of quite minor significance, they may on occasion produce considerable disability, from instability and locking This responds satisfactorily to removal of the offending tag, a minor orthopædic procedure In addition to its simplicity, this has the merit of saving the rheumatoid patient from fruitless exploration in search of a torn "posterior horn" or a cyst of the external cartilage These latter conditions receive more emphasis in standard textbooks, and therefore spring first to mind in the consideration of the difficult knee

It would appear from the article by Treanor et al [8] on unusual sites of presentation of rheumatoid arthritis that our experience here is not unique They mention cases in which surgical treatment of a solitary affected joint is advised, the real diagnosis being considered only after this fails to cure Grokoest

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1 *Lancet*, 1957, i, 379
2 Hinson, K F W, Moon, A J, Plummer, N S *Thorax*, 1952, 7, 317
3 Snapper, I *J Amer med Ass* 1947, 133, 157
4 Snapper I *J Mt Sinai Hosp* 1948, 15, 156
5 Loge, J P, Rundles R W *Blood*, 1949, 4, 201
6 Boyd W Text book of Pathology, p 907 London, 1953
7 *Lancet*, 1957, ii, 1209
8 Treanor, W J, Grant, A E, Psaki, R D *Arch phys Med Rehab* 1956, 37, 699

et al [9] recently reviewed 110 patients with juvenile rheumatoid arthritis, and found that 39% had monarticular onset In *none* of these was the diagnosis of rheumatoid arthritis mentioned during the initial evaluation

This stimulated Mr Peters, an Otago medical student who was working here, to review our own cases of juvenile rheumatoid arthritis He found that 38% of our patients had a monarticular onset recorded in their histories Again, none of these children had been originally diagnosed as rheumatoid arthritis

Queen Elizabeth Hospital,
Rotorua, New Zealand.
B S Rose

Parliament

Artificial Insemination

The debate in the House of Lords on Feb 26 on this subject was not confined to Lord Blackford's narrow motion that artificial insemination of a married woman by a donor other than her husband is tantamount to adultery, but ranged freely over the moral, medical, and legal difficulties with which the practice is beset.

Lord Blackford himself opened the debate by offering some facts and figures This, he admitted, was not easy because of the cloak-and-dagger secrecy with which the procedure was surrounded. No doubt there had been isolated instances ever since John Hunter in 1790 produced by this means a baby for a linen-draper's wife But as a recognised branch of medical practice it went back only some twenty years In 1938 a small group of scientists and doctors was formed under the ægis of the late Sir William Gilliatt and the late Sir Charles Read to experiment in this operation. The group broke up after ten years because its members had come to the conclusion that their experiments were bad from the point of view of the child and because so many of the couples who approached them were unsuited to become parents Lord Blackford had been unable to ascertain how many babies had been produced during those years, but he had been told that they "reached three figures " Other doctors had practised privately since, and estimates of the number of children produced ranged from 5000 to 10,000

Turning to some of the problems the procedure created, Lord Blackford said that. though it might gratify the wishes of the husband and wife, it took no account of its effect on the family and the child He thought that A.I D should be discouraged, and he used the word advisedly, because he realised that A.I D had come to stay and that we must adjust ourselves to its difficulties and perplexities He was certainly against making it a criminal offence. One way of discouraging it would be to insist on the registration of donors A system of licensing a certain number of practitioners who might carry out the operation would also limit its use.

CRITERIA AND CONSPIRACY

The Archbishop of York said that, though he held A.I D to be thoroughly wrong, he was bound to acknowledge that high motives of doing good to unhappy people were conspicuous among those who practised it, and that doctors wrote with a great sense of responsibility about the conditions in which it was right to undertake the operation But the fair-sized volume of testimony which had accumulated showed a vast discrepancy as to what the principles of this ethical control were The tangle of inconsistencies made it impossible to believe that any one agreed theory as to what was the right occasion for granting A I D could control the practice. He himself did not believe that there could ever be a right occasion He did not think it would be wise to make A.I D a criminal offence, but it was urgent to eliminate in the public mind any shred of an idea that A I D could somehow be made to lie within the marriage bond

Lord Denning said that some doctors thought that there was no law against this practice, and if it was done openly and without concealment this was true But if it was accompanied by secrecy and deception, he held that it was a criminal conspiracy Even if the husband consented, was it not a potential fraud on others? For the child, in his view, was illegitimate A false statement in the register of births was perjury He thought there was a double unlawful conspiracy—by the doctor with the wife and by the doctor with the donor Not only was that so in criminal law, but also it could give rise to damages by any person injured by it. To Lord Denning it seemed that if the practice became widespread it would strike at the stability and security of family life. He would say to the doctors, "Where by your science are you leading us? Seek to relieve suffering by all means, but do not do it by secrecy and deception "

Lord Amulree thought that the number of A.I D births was going to be a tiny drop in a big ocean. He thought the estimates given were on the large side A doctor who had been using this operation for twenty-five years told him that he had seen 2500 sterile couples of whom only 200 were considered suitable for A.I D and the number of successes had been about 100 The work, he thought, should be kept in the hands of doctors who should be able to use certain criteria The doctor must know the parents well, and be satisfied that the marriage was stable, and that a child was really wanted As the work had been going on for only twenty-five years it was hard to judge what became of the children, but so far the records showed that they appeared normal and had turned out satisfactorily Lord Amulree deplored any suggestion that artificial insemination should be made a crime. The one thing to make it safe was that it should be carried out freely by responsible people To make it subject to rules and regulations would be to drive it underground and have it done by charlatans and quacks In his speech Lord Chorley also took up this point, and said that it would be most unfortunate, for it might lead to the use of inferior donors and poor progeny

IN WHOSE HANDS?

The Bishop of Exeter said that though he had signed the report of the Archbishop's Commission which had recommended that A I D should be made a criminal offence, he would not sign it today Such a step, he was now convinced, would have the effect of drawing its practice from the responsible hands in which it now rested to totally irresponsible, possibly disreputable hands, as had happened with abortion, and might open the door to a fiendish type of blackmail. Furthermore, if A.I D were made a criminal offence it would presumably make the children certainly illegitimate, which would press unfairly on the only really innocent party In his view it would be better to institute a system of control and regulation by which only a panel of selected doctors should be allowed to practise A I D and that anyone else doing so should be guilty of a criminal offence The panel of doctors should be empowered to test every donor carefully for suitability, it should give A I D only to married women with the husband's consent, and the fact of the A.I D should be registered at Somerset House or on the birth certificate He was uncertain how far secrecy about the identity of the donor was really necessary this was a matter for further investigation Secrecy as to the fact that A I.D had been used meant that the whole life of the family was based on a living deception, and it would be better to get rid of it and of the unmistakable element of furtiveness that at present surrounded the whole business He reiterated that in his view A I D was against the law of God Wife donor, consenting husband, and doctor were sinful only the child was innocent To those who could not accept that judgment he would say " If you really believe that A.I D is right, then do it openly and without shame Be rid of pretence and deception Accept the necessity of open registration "

The Archbishop of Canterbury said that if we went on as we had done for the past nine years, talking occasionally about the subject and doing nothing by sheer inadvertence and inertia the habit would be established as part of the social life of the country He wished to make it plain that the Church of England had no objection to artificial insemination with the husband's semen, which they regarded as a method of helping the fulfilment of one of the main purposes of marriage But the use of donor semen was utterly different, it involved in falsehood and deception the husband, the mother, the donor, and the doctor, who (however highminded he might be) not only connived at a perjured declaration of birth, but also made the supposed father and mother promise to conceal the truth forever from the child and from society To him it was strange that the medical profession should have been content that some of its members, on their own individual authority, should take the law out of the hands of Church and State—into their own hands He would suppose that the profession itself would desire authoritative clarification of what may or may not lawfully be done

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[9] Grokoest A. W, Snyder, A. I, Ragan C. *Bull. rheum. Dis* 1957, 8

He asked the Government to act in this matter without delay He himself thought that the action should be prevention or registration, but the Government might not wish to go so far Whatever action was taken, we need not fear that the law would be unworkable For the medical profession, he was confident, would accept scrupulously as a matter of professional honour what the law decreed Let this practice, he said, be driven underground, as abortion is, and no responsible doctor would practise it He would expect the medical profession to welcome a step that would relieve them of a spiritual, moral, and social responsibility which did not belong to the medical profession alone He felt that, though the profession was honoured and respected beyond expression, its members must not (and only a few of them did) arrogate to themselves the right to settle a matter of such profound spiritual and moral significance

Viscount Kilmuir, the Lord Chancellor, said that it was reasonable to suppose that more information about the practice of insemination was now available than in 1948 when the Archbishop's Commission reported Yet the debate had shown that a great deal about the practice and its effects was still largely unknown except to the few who were closely associated with it Great care must be taken before making a law creating a fresh criminal offence or before adopting the principle of registration In the Government's view the factual information which we had was insufficient and in view of the difficult problems and the acute differences of opinion to which the practice gave rise, they had decided to set up a small inter-departmental committee to inquire into it and make recommendations

N H S. Contribution

Mr **J E S Simon**, financial secretary to the Treasury, on Feb 25 moved a resolution in the Committee of Ways and Means to increase the rates of contributions to the National Health Service in accordance with the announcement made by the Chancellor[1] He pointed out that since last year the health service contribution, unlike the National Insurance contribution, had not ranked as a deduction from income assessable to tax, the increase would therefore fall equally on those who paid tax and those who did not He agreed that it was inherent in any system of flat-rate contributions that they fell most heavily on the lower-paid worker But the increase of *6d* a week for an employed man, for instance, must be viewed against average weekly earnings of £12 *11s 7d* The increase in the contribution since 1948 was *1s 2d* while the increase in average earnings was £5 10s We must, he added, count not only the cost but also the benefits, and he asked members to look at the difference in the service since its start 27% more patients were being treated than in 1949, waiting-lists had been reduced, 6% more beds were available, hospital services had been improved, more research was undertaken, and more and better drugs were available The benefit of all this improved medical care to the citizen could be measured, among other things, by the years added to his life, reduced infant mortality, and the startling fall in the incidence of tuberculosis

Other members were less reassuring about the weight of the burden which the new contributions would throw on the lower-paid workers Miss **Margaret Herbison** pointed out that average wages did not mean a thing to a railway worker with a basic wage of £7 *7s* a week, an agricultural worker with a wage of £7 *10s*, or a woman in the retail food trade with a wage of £4 *17s 6d* With the new increase these people would have to pay out 6 75%, 6 6%, and 8% of their incomes respectively

The general feeling that the flat contribution had now reached its limit led several members to ask for a reconsideration of methods of financing the social services Mr **William Shepherd** reminded members of the Continental system by which, in France for example, the social services added about 50% to the wages bill and nothing came out of the Exchequer Mr **R P Hornby** pointed out that out of every £1 of Government expenditure for every *2s 1d* spent on health only *1s 8d* went on education The existing proportions were not necessarily the right ones Increased contributions were better than increased charges or a reduction in services, but he thought that the time had come to study the whole question of social service payments including sliding scales of contributions

Mr **Arthur Blenkinsop** wondered why the Government had decided to raise an extra £24 million On their own figures it seemed that the sum required was £9 million rather than £24 million He also wondered what was the right method of raising funds This increase could not be considered in isolation, for there had been three increases in the weekly contribution within the past nine months He thought that we had gone far beyond reasonable bounds in using the flat-rate method

Mr **Derek Walker-Smith**, the Minister of Health, said that the estimated gross cost for the N H S for 1958–59 of £740 million was £31 million more than the estimated out-turn for the current financial year, but it had been reached only by the most vigorous pruning The contributor in this country was getting a better bargain than the citizens of other countries and better than he could have expected in the early days of the service He could, surely, not unfairly be asked to pay a little more.

Fees for Cremation Certificates

On Feb 26 in an adjournment debate Mr **Dennis Howell** raised the question of the charges made by doctors in the National Health Service for the second medical certificate which is required before a body can be cremated Some doctors, he understood, would sign a certificate without a fee, some charged the two guineas recommended by the British Medical Association, others as much as four or six guineas Why, he asked, should there be any charge when these people were full-time employees of the health service?

Mr **Richard Thompson**, parliamentary secretary to the Ministry of Health, said that in 1949 it had been agreed between the medical profession and the health departments that though whole-time hospital doctors were debarred from private practice they might undertake for a fee some tasks not strictly within the scope of the hospital service, such as medical examinations not in the course of treatment for some purpose such as insurance or emigration The second certificate for cremation fell into this category The attention of the Royal Commission on Remuneration had been drawn to the fact that whole-time as well as part-time specialists may receive payment for services outside the scope of the N H S

As these fees were outside the N H S, the Minister of Health had no jurisdiction over them The Home Secretary had powers under the Cremation Act to regulate them, but so far he had not found it necessary to exercise his powers

Children With Ventricular Septal Defects

Mrs **Joyce Butler**, on the adjournment on Feb 28, asked what facilities there were for treating children with this disability in this country She gave particulars of six cases where the parents had found it difficult or impossible to arrange for their children to be treated in this country

Mr **Thompson** said that in some operations on the open heart hypothermia had proved so successful that it seemed unlikely that the lung-heart machine would continue to be used save in special cases such as these It was, however, available at

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[1] See *Lancet*, Feb 22, 1958, p 419

13 centres though the operation for interventricular septal defect had so far only been performed at 4 of them—Guy's Hospital, Westminster Hospital, Bristol Royal Infirmary, and the Royal Liverpool Children's Hospital The number of operations which had been carried out was not known, but it was certainly small, since the technique of the artificial circulation was new and there had been little opportunity for the teams to acquire experience in its use because so many patients here were treated by hypothermia Much greater experience had been acquired in the United States, where the heart-lung machine was more widely used, often in operations for which hypothermia would be chosen in this country But he would not take the view that we were unable with our facilities to do here what was done in the United States In some cases an operation could not be justified and there was a real risk of the children making fruitless journeys abroad The final decision in any individual case must be for the doctor

The Law and Suicide

Members of all parties have signed the motion, tabled in the Commons on Feb 27 by Mr Kenneth Robinson, that

> "this House is of the opinion that the present law of England relating to suicide has no deterrent effect, is capricious in its incidence, and can no longer be regarded as reflecting the attitude of society, and considers that suicide and attempted suicide should be removed from the category of criminal offences"

QUESTION TIME

Senior Registrars

Mr Kenneth Robinson asked the Minister of Health if he would make a statement on the decisions reached at the meeting of the Joint Consultants Committee held on Feb 27 to discuss the senior registrar problem Mr D Walker-Smith replied After a further discussion with officials, the representatives of the Joint Committee expressed a desire to discuss the subject with me I have intimated my readiness to meet them at an early date Mr Robinson Can the member say for how long this matter, which was urgent two and a half years ago, is going to drag on? How is it that this committee managed to complicate what is essentially quite a simple problem? Who are the stumbling-blocks to a solution—his department or the consultants? Mr Walker-Smith I am anxious to get an appropriate solution of this problem, the urgency of which I have already recognised in this House, by general agreement if at all possible, but an appropriate solution I must have in any event, and I have no doubt that the committee will take note of the interest of hon members on this subject

Mr J D Cronin Is it not the case that this meeting on Feb 27 reached a deadlock because the Minister wanted to make the setting up of the sub-consultant grade a condition for relieving the distress of the registrars?—Mr Walker-Smith No, I do not think that that represents a full or faithful precis of the committee's decision I am looking forward to seeing the committee myself and discussing the problem with it. I hope the hon gentleman does not dissent from what I apprehend is the general view of hon members, that there ought to be a solution to this problem, and pretty quickly, too

Admissions to Mental Hospitals

Dr Donald Johnson asked the Minister whether he was aware that the summary reception order providing for the certification of a person as of unsound mind and for the compulsory removal of that person to a mental hospital, which is in use under the provisions of the Lunacy Act, 1890, as amended, was of identical nature to that first used in the year 1853, and whether, in the light of the advances of medical science since that date, he would introduce regulations to alter this without delay Mr Walker-Smith I am considering the Royal Commission's recommendations for new procedures, which would require legislation.

Mrs Braddock While waiting to implement the recommendations of the Royal Commission, would not the Minister consider the possibility of proceeding in the first instance under the provisions of section 20 of the appropriate Act instead of section 16? Is he aware that that could be done without any new legislation and that the use of section 20, which puts a patient during the first three days into the hands of fully qualified psychiatrists in the observation unit, would in many cases meet criticisms about admissions at present made under section 16?—Mr Walker-Smith I will examine carefully the suggestion.

Certification of Mental Defectives

Mr Norman Dodds asked the Minister of Health if he was aware of the concern arising from the fact that there were 4455 mental defectives detained in mental-deficiency hospitals who were certified on the ground of being found neglected, when they were at the time and had been for some time previously in the care of homes of local authorities or an approved charitable organisation, and how many had been certified in this way during the years 1956 and 1957, respectively —Mr Derek Walker-Smith replied All these cases have been reviewed The answer to the second part of the question is None, since March 9, 1956, the date of the High Court judgment in Regina *v* Board of Control ex parte Rutty

Mr Dodds Is it not a fact that when these people get too old to remain in those homes we have been using the expedient of certifying them and sending them to mental institutions, because we have not provided more suitable places?—Mr Walker-Smith The Board of Control was following what had been the accepted practice until the judgment in the Rutty case Its difficulty now is that people cannot be discharged until there is somewhere appropriate for them to be discharged to Mr Arthur Blenkinsop Does not this information reinforce our demand that the Government should make up their mind about further financial assistance to enable local authorities to provide more accommodation in cases such as these?—Mr Walker-Smith It is a relevant factor in the determination of what should be done in the way of local authority accommodation, though there are other factors which also have to be taken into account

Whitley Again

Mr Kenneth Robinson asked the Minister whether he had now instructed his representatives on the Whitley Council which is considering the radiographers' salary claim —Mr Walker-Smith I have informed both sides of the Whitley Council that, in present economic circumstances, the Secretary of State for Scotland and I could not agree to a pay award being made in response to this claim Mr Robinson Is this not a further outrageous interference with the working of Whitley Council machinery?—Mr Walker-Smith On a previous occasion criticism was made that the Secretary of State and I did not give sufficient indication of the way in which our minds were working in regard to the exercise of our statutory duty In this case, we have given notice so that both sides of the Whitley Council are aware of the position Mr Robinson Is the Minister in fact saying that now every Whitley Council has got to reach disagreement before there can be even the possibility of a pay increase? Is that what this decision means?—Mr Walker-Smith No, Sir I am saying that these questions have got to be looked at on their merits in the context of the general economic position of the country

Medicine and Television

Sir Ian Clark Hutchison asked the Postmaster-General whether he was aware that many doctors believe that the television programme, *Your Life in Their Hands*, will have a bad effect on viewers, and if he would use his powers under section 15 (4) of the Licence and Agreement to instruct the British Broadcasting Corporation to refrain from showing this type of programme —Mr A E Marples I am aware that opinions differ about the merits of these programmes, but I see no reason to interfere with the independence of the B B C in making programmes

Sir I Clark Hutchison Does not the Minister think that this is rather a morbid type of programme? Will he consult representatives of medical opinion and consider this again?—Mr Marples I must emphasise that the B B C is responsible for the programme, and not the Postmaster-General As to consulting medical opinion, before the programme the B B C consulted the Royal College of Surgeons, the Royal College of Physicians, and the College of General Practitioners After the programme, those three colleges said that they appreciated the programme

Sir Hugh Linstead Does the Minister agree that the reaction from the public, as received by the B B C, has been almost entirely favourable to this programme ?—Mr Marples As far as I understand, there had been, up to Feb 20, very little reaction in the form of letters There were 25 letters approving and encouraging the programme, 6 suggesting additions to the service, and, I think, 7 suggesting that the programme is unsuitable

The House returned to this subject on Feb 27 when Dr Edith Summerskill raised it on the adjournment She contended that to have an interest in disease was not healthy unless one was a public-health worker A lay person had only a morbid interest in disease which these television films were fostering She accepted that intelligent men and women had looked at these films and said "How very interesting Yes, these should be very interesting to the viewing public" But a surgeon or physician interested in his own technique probably did not think how the films might hurt those who were not so intelligent or well-informed, and the fact was that T V today was viewed by a vast number of emotionally unstable people who identified themselves closely with the proceedings

Mr Kenneth Thompson, the Assistant Postmaster-General, admitted that the programmes were controversial, but he had more confidence than Dr Summerskill in the capacity of his fellow citizens to judge for themselves and to arrange their conduct in the light of that judgment It was true that for its own reasons the B B C did not consult the British Medical Association, but the Minister was not called on to express an opinion on the rights and wrongs of that In these things the B B C must have complete freedom Supposing the B B C had consulted the B M A, and the B M A had expressed the opinion which now appeared in the *British Medical Journal*, was the B B C then to allow the B M A to have the power of veto over its proposals ? This would surely place both bodies in an impossible position

His personal opinion, in which the Minister concurred, was that the programmes would do good rather than harm Some neurotics and hypochondriacs might react badly, but that applied also to other films and presentations on the B B C If one person was advised by these programmes to seek an early opinion and if one life was saved or one illness shortened, the B B C could claim that it had been instrumental in putting understanding in place of fear, information in place of mystery, and guidance where there was only doubt

N H S Visits

Under the National Health Service the average number of visits per patient is about 3 by the patient to the doctor and about 2 by the doctor to the patient

Medicine and the Law

Personality Change after Operation

A former teacher was charged with fraudulent conversion, and it was claimed that after an operation two years previously his personality had changed completely—from companionable to morose, according to his wife[1] A psychiatrist gave evidence that after the operation there was a complication that resulted in damage to the brain through lack of oxygen This damage caused a personality change, which might result in his losing his sense of responsibility and his memory for recent events The defendant was put on probation for three years on condition that he underwent a course of psychiatric treatment

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[1] *Times*, Feb 26, 1958

Obituary

JOSEPH GODWIN GREENFIELD

M D, B Sc, LL.D Edin, F R C P

Since his retirement in 1949 from the post of pathologist to the National Hospital, Queen Square, Dr Greenfield had worked from time to time in the United States, and it was at Bethesda, Maryland, that he died last Saturday at the age of 73

His father was W S Greenfield, F R C P, professor of pathology and clinical medicine at Edinburgh, and he was educated at Merchiston and Edinburgh University Qualifying in 1908, he was house-physician at Queen Square for a year or two before he went to the General Infirmary at Leeds as assistant pathologist in 1912 In 1914 he returned to the National Hospital as pathologist, but he held a commission in the R A M C until 1919 In that year he was writing with Farquhar Buzzard on encephalitis lethargica, and in 1921 they collaborated in their *Pathology of the Nervous System* He was making, and continued to make, fine use of his exceptional opportunities for working both individually and with clinicians, and among his later studies were contributions made with W J Adie, James Taylor, Purdon Martin, and E A Carmichael, and with American associates

As a teacher Greenfield exerted much influence through his books but even more through his daily contacts, alike with juniors and with coevals, for his qualities as a person matched his abilities as investigator and pathologist Some of these qualities and abilities are brought out by the following tributes from two of his friends

* * *

The sudden and unexpected death of Godwin Greenfield, in what seemed a singularly youthful and robust old age, marks far more for his friends and colleagues than the passing of a great figure in the world of neuropathology Not soon shall we see again a man in whom were so happily blended so many qualities a lightly-worn but *immense* erudition in his subject, a record of major contribution to it, a generosity unsurpassed in the giving of the fruits of his experience to other workers, a complete unselfishness, with a modesty and equanimity and an integrity that made it not possible for him to have an enemy, and that gained for him a widespread personal affection and respect A more rounded and complete personality it would have been hard to find, and those who enjoyed the privilege of his friendship, as colleagues or as pupils, will not forget him Good nature he had in abundance, but no gifts of eloquence, and it was in personal conversation and teaching that he made his greatest impact upon his pupils and upon all who sought his advice or help

My own valued friendship with Greenfield began in 1912 when we were both in residence in the National Hospital, Queen Square From this hospital he moved to Leeds to learn the discipline of pathology, that he was to follow, from that great teacher, *Matthew Stewart*, professor of pathology at Leeds The first war ended, Greenfield returned as its first whole-time pathologist to Queen Square, and there with limited resources, and with still narrower material reward, he began that unbroken course of original contributions to neuropathology upon which he was still engaged up to the time of his death These contributions appeared in *Brain* and other journals over the years, and there are few pathological processes within the nervous system that have not been studied and illuminated by him Even to enumerate all the special problems which have occupied him would be beyond the scope of this notice Yet there should be mentioned his textbook (with Buzzard) of neuropathology, his monograph (with Arnold Carmichael) upon the cerebrospinal fluid, his recent work on the pathology of muscle (with American colleagues), and an as yet unpublished work on neuropathology

In addition to all this he bore the burden for many years of all the routine morbid-anatomical and clinical pathological work of the hospital, and the training of a sequence of young men in the methods of morbid histology and anatomy of the nervous system

In the United States his reputation stood particularly high and after his retirement on reaching the age-limit in this country he was eagerly invited to continue his work in the National Institute of Neurological Diseases and Blindness at Bethesda, Maryland. There during three long visits he did some of his best work in a country not his own, where a rational flexibility of administration, and a sound appreciation of his capacity still to add to knowledge, made it possible to find the resources for an emeritus to continue to utilise his gifts in the service of mankind

Every man who knew him was Greenfield's friend, and he well deserved the esteem in which he was held Public and academic honours did not come his way, save for the honorary degree which his own university, Edinburgh, conferred upon him in 1956 Yet we should go far to find a man who merited them more Greenfield was too modest for this world, but he could not but have been aware of the warmth of regard in which he was held by those able to appreciate him and his work, and we may be sure he was well content with what so few of us can hope to deserve or to obtain in such full measure Not less happy was he in his family, and to Mrs Greenfield, the gracious partaker of his many virtues, and to his family our deepest sympathy goes out in their loss

F M R W

The debt owed by pathologists, and neuropathologists in particular, to Godwin Greenfield is great both in this country and abroad. For over the years his laboratory at Queen Square was frequented by a succession of young people from other countries who came to the National Hospital for neurological training They received unlimited teaching and advice from a man who had trained himself not only in the techniques for which this centre has been famous but in the interpretation of what is seen under the microscope in terms of observed symptoms and signs during life The attachments formed between teacher and pupil were such that few can have enjoyed the continued friendship and admiration of so widely dispersed a community throughout the world.

Until about ten years ago the neuropathologists of this country could be numbered on the fingers of one hand The formation then of a number of new posts for workers in this field led to the recruitment of young people all eager but with much to learn. Characteristically Greenfield recognised their need, he called a preliminary meeting of those interested, and at Queen Square a "Neuropathological Club" was formed which aimed at providing a forum for the discussion of difficult problems Soon its membership was extended overseas, where isolated workers in particular were glad to join this new fraternity There are now 45 home members and 15 from abroad This club will be a living and lasting memorial to an important side of Greenfield's professional activities

His enthusiasm was at all times stimulating and infectious, whether he was discussing such obscure topics as carcinomatous neuropathy, or his outside interests and hobbies which were varied He was a keen gardener, and visitors to his home at Westcott would be taken on tour round his large and beautiful garden. Pausing before various, often rather exotic, trees and shrubs he would enlarge upon the attributes of each silent friend, occasionally perhaps lament its pathology His appreciation of beauty also found expression in photography, and in recent years visitors to Westcott often had the chance of enjoying projected 'Kodachromes' of his travels· views in which intrinsic merits of colour and form were most memorable.

In research Greenfield's inquiries covered many applications of general and special pathology to the central nervous system, as witnessed by his publications He was perhaps best known as an authority upon the different forms of encephalomyelitis, but it would be difficult to name any aspect of neuropathology upon which he was silent. It is gratifying to know that much of his knowledge will be crystallised in a volume to be issued within the next few weeks This and other tangible products of the years of his retirement will be cherished by the many who have enjoyed his comradeship and help, but are left to mourn his departure

D S R

Dr. WILKIE SCOTT

I M L writes

I knew Dr Scott for some years and had the privilege of working with him in Nottingham I shall always remember him as a kindly, courteous man, humble enough to admit when he was wrong, and generous to his younger colleagues He had a dry sense of humour, strongly tinged with the background of his native Scotland The tragic loss of his wife must have been a blow from which he never really recovered.

Dr. ALFRED BENATT

A friend writes

Benatt received his training and early inspiration in the clinic of a medical genius and humanist—Frederic Kraus in Berlin It was here that his scientific gifts and leanings were directed to cardiology He early felt that cardiology should provide the scientific basis for balneology, and his extensive and successful work to that end should be remembered At the same time he had a deep sense of historical continuity and he looked at some of his problems and subjects in historical perspective It was in this spirit that he made a scientific pilgrimage to the ancient and highly interesting watering-places of Anatolia and that he was able to illuminate the early history of cardiac catheterisation, reviving the work of the ingenious but forgotten Berlin clinician Bleichroeder His masterly survey in connection with his own work on tuberculosis in Thailand reflects the vision and insight into human relationships which are taught by medical history

Intensely keen on refreshing, deepening, and extending his knowledge, Benatt would miss no meeting, demonstration, or discussion, near or far This in itself showed an essential modesty and readiness to compromise—although at first sight and to some he might have given a different impression He took a great interest in the progress of those young specialists who, on returning from the war, took up their studies for higher qualifications, and this interest was highly appreciated He was exceptional in the trouble that he was prepared to take on behalf of his patients and friends

The work he later did in Italy, Thailand, North Africa, and elsewhere revealed the aptitude, adventurous streak, and quiet heroism of the pioneer

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Births, Marriages, and Deaths

BIRTH

EVANS —On Feb 4 at St. Bartholomew's Hospital, E.C.1, to Muriel, wife of Robert J Evans, M.D —a son Miles Liddard.

HUGHES —On Feb 24 to June wife of Edward Brerley Hughes—a daughter

DEATHS

HOWAT —On Feb 9, in London, Robert King Howat M.B Glasg , F R C S , F.R.F P S

Notes and News

A WORKSHOP FOR MENTAL PATIENTS

We lately referred[1] to the grant of £7500 made by the Nuffield Provincial Hospitals Trust to Cheadle Royal Hospital, towards the running costs for three years of a sheltered workshop It is hard to fill the time of long-stay patients constructively and therapeutically, and Dr W V Wadsworth, medical superintendent of Cheadle Royal, felt that work in hospital departments or gardens was unsatisfactory, because patients were rarely made to feel valuable or responsible Whether the work was well or ill done made little difference, and enthusiasm was seldom generated Moreover, the rewards were unrelated to the work done As part of a general modernisation of the hospital and an "open doors" policy, a new occupational centre was built,[2] but the tempo of work done there was slow and unsteady, and the handicrafts practised seemed inadequate to sustain interest Something closer to an ordinary factory was needed

After visiting mental hospitals in Holland and certain industrial concerns, Dr Wadsworth decided to incorporate two new principles into the proposed hospital industrial unit healthy people from outside should be employed alongside the patients, and the product should be marketed by the hospital and the receipts devoted to paying the patients and supporting research connected with the workshop The healthy workers would make it possible to cope with fluctuations in demand, yet leave an uninterrupted flow of work for the patients

It is intended that the workshop, which was conceived as part of the treatment offered by the hospital, will be so sheltered that the tempo of work can be adapted to clinical indications and the changing pressure in demand buffered It will help to instil an increasing sense of independence, which will later be encouraged by the establishment of a hostel, and perhaps by work outside the hospital The products of the workshop will be paper novelties and decorations, which are in demand not only at Christmas but also in the summer—in holiday camps, for example The profit is expected to be enough to pay slow workers a worth-while wage, to make the workshop self-supporting in three years, and to assist in the maintenance of the proposed hostel

Although it is hoped to avoid a "research atmosphere", some investigations are planned as a by-product of the work of the shop For example, the effects on patients of the proximity of healthy workers, of varying degrees of strictness in supervision, and of pay differentials and target schemes, the effects on production of the visual and auditory environment and of clinical conditions, and the clinical effects on patients of doing such work, could all be investigated in controlled schemes

The grant will pay the salaries of an industrial psychologist in charge of the investigations and of an industrial manager, and leave a margin for equipment

SCIENCE AND POLITICS

In his Bernard Dyer lecture to the Society for Analytical Chemistry, Sir Hugh Linstead, M P, secretary to the Pharmaceutical Society, spoke of the political responsibilities of scientists They must not only discover new things but interpret them—both to the politicians, who had the duty of applying scientific discoveries to daily affairs, and to the man in the street, by whose consent the politician governs The public are eager to learn, but are often disappointed because science has given them so many miracles that they have become insatiable and will not believe that no answer can be given to some questions The meaning of the discoveries must be explained in the passionate images that alone will hold attention but illuminated only by the cold objective light of scientific truth

But the scientist, Sir Hugh continued, should preserve his independence by holding aloof, like a public servant, from all political parties He cited Lord Halsbury as acknowledging that this was no negligible request to make of scientists, many of whom held strong and sincere political views, but he believed that the things lost were more than compensated for by the contribution they made to the moral store of humanity

Sir Hugh said that Julien Benda, in *La Trahison des Clercs*, has accused the scientist along with other intellectuals, and asserted that certain fundamental standards and truths (such as the objectivity of science) are at present in danger, and that the intellectual's duty is to protect these at all costs This entailed his keeping himself clear of the compromises and temptations of politics The intellectual himself might be crucified, said Benda, but his words would haunt the memory of men till they prevailed

NATIONAL CORPORATION FOR THE CARE OF OLD PEOPLE

There is something about round figures which prompts us all to self-examination, and the tenth annual report[1] of the Corporation shows how useful decennial reflection can be Since it was started in 1947 it has distributed over £1,200,000 for work among old people Much of the money has gone as grants-in-aid to voluntary organisations, for the governors believe that it is their job to help voluntary bodies to experiment with small informal pilot schemes, some of which, when proved and tried, will take their place on the more formal pattern of statutory provisions Housing, chiropody services, domiciliary care have all claimed the Corporation's interest and generous support in the past, in the future the governors probably will not have so much money to spend and will have to be more selective though no less willing to help Their work among so many voluntary and statutory organisations in all parts of the country has suggested to them that there is need for a central information exchange Many useful local schemes are started without the knowledge that elsewhere similar schemes are being tried which could offer advice based on early experience, valuable surveys are undertaken and the information collected receives only local publicity The Corporation therefore propose to compile and maintain a record of what is being done for old people all over the United Kingdom, and later perhaps abroad, and to carry out inquiries and research projects

In their report last year[2] the Corporation gave some figures which suggested that it was not necessarily cheaper for old people to remain at home with the support of domiciliary services This year they give some more budgets, but the evidence still seems inconclusive and clearly much more information is needed Perhaps the new clearing-house could collect it

MEDICAL SPECIALISATION AND THE LAW

The increase in the number both of specialists (who may outnumber the general practitioners) and of specialties (up to fifty are recognised in some countries) reflects increasing medical sophistication Protection of the public against the unqualified setting up as specialists is usually in the hands of the profession, who set up standards and prescribe suitable training and qualifications, but the tendency is increasing for control by legislation, and the present position is surveyed in a W H O pamphlet[3] An account is given of the laws in the 23 countries where specialisation is controlled by law, including definitions (or lack of them), periods of training, examinations, and registration

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Expansion of School Health Service in Birmingham

Birmingham Education Committee has approved a resolution to make the city's school health services available to children attending private schools in Birmingham

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[1] See *Lancet*, Feb 22, 1958, p 422

[2] *ibid* 1957, ii, 33

[1] The National Corporation for the Care of Old People Nuffield Lodge, Regent s Park, London, N W 1 10th annual *report* of the Board of Governors for the year ended Sept 30, 1957

[2] See *Lancet*, 1957, i 465

[3] Medical Specialisation a Survey of Existing Legislation World Health Organisation Geneva 1958 Pp 39 1s 9*d* Obtainable from H M Stationery Office, P O Box 569, London S E 1

University of Cambridge

On Feb 22 the following degrees were conferred

M.D —R W Ross Russell
Sc.D —Hermann Lehmann
M.B —R A S Gilchrist, E W R. Oakden (by proxy)

University of London

On Jan 1 the following degrees were conferred

D Sc —W R. S Doll
Ph.D —B K Acharya

University of Sheffield

Prof W Hobson has resigned from the chair of social and industrial medicine on his appointment as medical officer in training and education in the World Health Organisation regional office at Copenhagen Dr F I N Dunsford has been appointed part-time honorary lecturer in blood-group genetics

University of Cape Town

Dr J E Kench, senior lecturer in chemical pathology in the University of Manchester, has been appointed to the chair of chemical pathology on the joint medical staff at Cape Town University

Harveian Society

On Wednesday, March 19, at 11, Chandos Street, London, W 1, at 8 15 P M Prof Robert Kark will give the Harveian lecture To mark the centenary of Richard Bright's death he has chosen as his subject Bright's Disease, Then and Now

International Congress of Paediatrics

This congress will be held in Montreal from July 19 to 25, 1959 Further details may be had from the secretary-general, P O Box 215, Westmount, Montreal, Canada

International Congress of History of Medicine

This congress will take place in Montpellier from Sept 22 to 28 Further particulars may be had from the secretary-general of the congress, Faculte de Medecine, Montpellier, France

Euthanasia Society

On Thursday, March 13, at 7 30 P M, at Friends' Meeting House, Euston Road, London, N W 1, Dr Eliot Slater will speak on the biologist and the fear of death

Royal Society of Health

On Monday, March 10, at 2 30 P M, in the Caxton Hall, Westminster, S W 1, this society will hold a meeting on nuclear radiation hazards The speakers will include Sir Ernest Rock Carling and Dr W H P Minto

Ernest and Minnie Dawson Cancer Trust

The trustees have awarded the following prizes for 1956 £1000 to Dr J J Coghlan and £500 to Dr E C Atkinson The competition was open to general practitioners in Lancashire or Yorkshire for a thesis on cancer The closing date for the next competition is May 1, 1959 Further particulars can be had from the clerk of the trust, 89a, Fishergate Hill, Preston, Lancs

Association of Surgeons of Great Britain and Ireland

The annual meeting of this association will be held from April 10 to 12 in the Institute of Clinical Science, Grosvenor Road, Belfast The programme will include short papers on liver surgery, and Sir John Cockcroft will give the Mitchell lecture on radioactive isotopes Tickets may be had, not later than March 29, from the secretary of the association, 47, Lincoln's Inn Fields, London, W C 2

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold public hearings at the North British Hotel, Edinburgh, next week On Thursday, March 13, representatives of the Royal Faculty of Physicians and Surgeons of Glasgow have been invited to attend at 2 45 P M, and on Friday, March 14, representatives of the Royal College of Surgeons of Edinburgh at 10 30 A M and of the Royal College of Physicians of Edinburgh at 2 30 P M

Royal College of Surgeons of England

The Lister festival dinner, which takes place triennially, will be held at the college on Friday, March 28, at 7 45 P M Fellows may apply for tickets (50*s*) to Mr W F Davis, deputy secretary of the college, Lincoln's Inn Fields, London, W C 2

Royal Society of Arts

On Wednesday, March 12, at 2 30 P M, at the society, John Adam Street, London, W C 2, Mr N W Pirie will give the E Frankland Armstrong lecture on world hunger as a biochemical problem

World Congress of Prophylactic Medicine and Social Hygiene

This congress will be held at Merano, Italy, from Oct 18 to 23 Further particulars may be had from the general secretary, VIII, Piaristengasse 41, Vienna, Austria

Society for Psychosomatic Research

A conference on the nature of stress disorder is being held at the Royal College of Physicians, Pall Mall East, London, S W 1, from May 2 to 4 A few places are still open, and applications should be sent to the secretary of the society, 130, Harley Street, W 1

Regrouping of Water Undertakings

The Minister of Housing and Local Government is to make an order under which the water-supplies of Herefordshire will be reorganised (*Times*, March 4) A joint board covering nearly all the county will replace a number of existing water authorities This is the first compulsory order for regrouping water undertakings under the Water Act, 1945

Fact and Faith Film

Doctors in London were last week invited to see *Red River of Life*, an American film shown by Fact and Faith Films (12, Queen Anne's Gate, S W 1) It deals in popular terms with the functions of the blood and the mechanisms of the circulation, and suggests that the facts presented are evidence for the existence of a Creator It is one of a series of films presenting scientific advances from a Christian standpoint

Contraceptive Technique

A lecture film demonstration for final-year students from London medical schools will be given at University College Hospital Medical School, W C 1, on Friday, March 14, at 5 30 P M Prof W C W Nixon will be in the chair and Dr Sylvia Dawkins will speak Admission by ticket only from the secretary, Family Planning Association, 64, Sloane Street, S W 1

Prof Boris Petrov, Prof Isaac Zhorov, and Prof Vladimir Pshenichnikov have arrived from Moscow, at the joint invitation of the Faculty of Anæsthetists of the Royal College of Surgeons of England and of the British Council s Soviet Relations Committee, for a three weeks visit to study the methods and teaching of anæsthetics here They will visit hospitals at Oxford, Cardiff, Birmingham, Edinburgh, Newcastle, Liverpool, East Grinstead, and London

The muscular dystrophy group of the Central Council for the Care of Cripples has collected over £12,000 since it was founded two years ago Grants for research have already been made to support work in London, Oxford, Edinburgh, Newcastle upon Tyne, and Birmingham Applications for grants from workers who are studying normal or diseased human muscle should be sent to the group, 34, Eccleston Square, London, S W 1

Surgeon Rear-Admiral D F Walsh and Surgeon Captain George Phillips, R N, have been appointed honorary surgeons to the Queen, and Surgeon Captain W P E McIntyre, R N, an honorary physician

The late Sir Thomas Dunhill has left an estate in Great Britain valued at £138,163 gross His bequests include £3000 to St Bartholomew s Hospital Medical College for the benefit of the surgical professorial unit £500 to the Royal College of Surgeons of England, and £A500 to the Royal Australasian College of Surgeons

On Feb 25 the Liverpool Medical Institution presented Lord Cohen of Birkenhead with his portrait, which has been painted by Mr Harold Knight, R A The presentation was made by Prof Bryan McFarland

The Medical Historical Club of Toronto plans to erect a cairn in memory of Sir William Osler at Bond Head, the Canadian village where he was born Contributions are invited and should be sent to the secretary of the club, Dr Eric Linell, 253, Blythwood Road, Toronto 12, Ontario

Dr Lennox Johnston has been elected president of the National Society of Non-Smokers He will deliver his inaugural address, entitled Militant Non-Smoking, at Caxton Hall, Westminster, at 8 P M on Tuesday, March 11 Doctors are invited to attend

Dr John Bowlby has written, for the National Association for Mental Health, a booklet about separation of mother and child, and how it may be avoided or, if unavoidable, accomplished with least harm (Can I Leave my Baby ? Published by the National Association for Mental Health, 39, Queen Anne Street, London, W 1 Pp 14 1*s* 6*d*)

A series of 35 mm filmstrips has been produced by Messrs Reckitt & Sons, Pharmaceutical Department, Hull They deal with the care of the premature baby at home, the care of the geriatric patient at home, an emergency obstetric unit, the technique of blood-transfusion, the technique of ward dressing, the Rideal-Walker test, and the Chick-Martin test Each filmstrip is in colour and contains from 15 to 42 frames, that on blood-transfusion is in 2 parts A commentary is supplied with each The cost ranges from 30*s* to 42*s*

Appointments

Bannerman, Hugh, M B Durh, D O M S ophthalmologist, Bristol clinical area
Barclay, R F, M B Lond, D P H M O H, Kingswood, Mangotsfield, Sodbury, and Warmley, Gloucestershire
Coulsting, H S, M B Manc, D P M consultant psychiatrist (child guidance), Bristol clinical area
Everall, J D, M R C P honorary dermatologist, French Hospital and Dispensary, London
Pathy, M S, M R C P E assistant physician (geriatrics) (S H M O), Amersham General Hospital, High Wycombe, and Aylesbury Hospitals

Surrey County Council

Bartlett, P A, M B Lond assistant M O (school health, maternity and child welfare)
Battey, Alison M, M B Edin, D P H assistant M O (school health, maternity and child welfare)
Lilliott, Mairead M, M B Lond, D Obst, D P H assistant M O (school health, maternity and child welfare)

Birmingham Regional Hospital Board

Baker, H de C, M D Manc part-time consultant pathologist, Dudley and Stourbridge group of hospitals
Clark, J M, M B Lond part-time S H M O in venereology, Coventry group of hospitals
Garrett, J V, D M Oxon, D C P consultant pathologist, Birmingham (Selly Oak) group of hospitals
Irwin, D B, M D Lond, M R C P consultant gerontologist, Shrewsbury group of hospitals
Kelsey, Charles, M B Polish Med Sch, Edin senior casualty officer, Coventry group of hospitals
Riley, Harold, M B Leeds, D O M S part-time consultant ophthalmologist, Coventry group of hospitals
Smith, Helen E, M D Manc, D P H, D P M part-time S H M O in venereology, Coventry group of hospitals
White, I C, M R C S assistant psychiatrist (S H M O), Birmingham (mental A) group of hospitals
Wightman, David, M B Glasg senior casualty officer, Dudley and Stourbridge group of hospitals

Colonial Appointments

Balgobin, G L, M B Belf, D P H senior M O H, Mauritius
Blackman, Victor, M B Lond, D P H pathologist, Tanganyika
Digues la Touche, D M, M B Lond, D P H M O (grade B), public health, Trinidad
Draper, C C, B M Oxon, D T M & H, D P H medical research officer (grade I), East Africa High Commission
Dudds, V E, M B M O, Northern Nigeria
Easby, F P D, M R C.S M O (grade A), Government Hospital, Barbados
Fieldus, P L, M D Lond M O, Northern Rhodesia
Gillies, M T, M B Cantab, D T M & H medical research officer (grade I) entomologist, Malaria Institute, Tanganyika
Glyn-Evans, T, M B M O, Sarawak
Lorde, G M, L R C P E assistant M O, St Lucia
McCourt, J F, M B N U I, D.P H M O (special grade), Kenya
Nicholson, Velta S, M R C S, D P H M O H, Jamaica
Patel, R C, M.S Bombay, F R C S M O surgeon (grade B), health department, Trinidad
Pringle, Gordon, M B Durh, D T M & H senior medical research officer, East Africa High Commission
Raw, D R, M B Lpool M O, Kenya
Wallace, E H, M B Glasg, D O specialist ophthalmologist, Sarawak

Diary of the Week

MARCH 9 TO 15

Monday, 10th

University of London
5 30 P M (London Hospital Medical College, Turner Street, E 1) Prof W Wilbrandt (Berne) The Concept of Carrier Transports
University College, Gower Street, W C 1
5 P M Dr J D Judah Oxidative Phosphorylation Historical and Experimental (First of two lectures)
Postgraduate Medical School, Ducane Road, W 12
4 P M Dr Paul Fourman Symptoms of Thirst and Polyuria

Tuesday, 11th

Royal College of Physicians of London, Pall Mall East, S W 1
5 P M Dr Michael Kremer Sitting, Standing, and Walking (First of two Oliver-Sharpey lectures)
University of London
5 30 P.M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Prof H Hamperl (Bonn) Problems of Pneumocystis-pneumonia and Interstitial Pneumonia
Royal Society of Medicine, 1, Wimpole Street, W 1
5.30 P M *Experimental Medicine and Therapeutics* Prof J V Dacie Acquired Hæmolytic Anæmia (Presidential address)
8 P M *Psychiatry* Dr Felix Post, Mrs I Linker Prognosis of Old age Depression
St Mary's Hospital Medical School, W 2
5 P M Mr Aleck Bourne Postmenopausal Hæmorrhage
Institute of Dermatology, Lisle Street, W C 2
5 30 P M Mr A K Monro Venous Leg Ulcers
Institute of Laryngology and Otology, 330, Gray's Inn Road, W C 1
5 30 P M Prof F C Ormerod Development of the Internal Ear
Birmingham Medical Institute, Highfield Road, Edgbaston
8 P M *Psychiatry* Dr S H Foulkes Group Psychotherapy
Manchester Medical Society
8 P M *Surgery* (*Clinical Sciences Building, York Place, Manchester, 13*) Mr John Hewet Perinephric Abscess Mr G R Carr Carpal Tunnel Syndrome Mr Kenneth Bloor Cervico-thoracic Ganglionectomy

Wednesday, 12th

Royal Society of Medicine
4 30 P M *Physical Medicine* Dr Philippe Bauwens On the Fringe of Electrodiagnosis (Samuel Hyde lecture)
Postgraduate Medical School
2 P M Dr J G Leopold Pathology of Bronchitis and Emphysema
Institute of Dermatology
5 30 P M Dr Henry Haber Squamous Cell Carcinomata and Premalignant Conditions
Institute of Neurology, National Hospital, Queen Square, W C 1
5 30 P M Dr W W Payne Calcium and Phosphorus Metabolism as Involved in Nervous Disorders
Oxford University
5 P M (Radcliffe Infirmary) Dr C W Taylor Value and Limitations of Laboratory Investigations in *Gynæcology* (Litchfield lecture)
Manchester Medical Society
4 30 P M *Pathology* (Medical School) Dr A L Latner Intrinsic Factor and Vitamin B_{12} Absorption
Royal Faculty of Physicians and Surgeons of Glasgow, 242, St Vincent Street, Glasgow
5 P M Dr J A Simpson Modern Methods of Electrical Diagnosis in Neurological Disease (Watson lecture)

Thursday, 13th

Royal College of Physicians of London
5 P M Dr Kremer Sitting, Standing, and Walking (Second of two Oliver-Sharpey lectures)
University of London
5 30 P M (*London School of Hygiene* and Tropical Medicine) Prof Kurt Mothes (Berlin) Physiology of Alkaloids (First of two lectures)
Royal Society of Medicine
5 P M *Ophthalmology* Dr F O MacCallum, Mr B R Jones Virus *Diseases of the Cornea*
Institute of Dermatology
5 30 P M Mr Monro Treatment of Skin Tumours
Alfred Adler Medical Society and Adlerian Society of Great Britain
8 P M (1, Wimpole Street, W 1) Dr R Dreikurs (Chicago) A New *Concept of Man*
Liverpool Medical Institution, 114, Mount Pleasant, Liverpool, 3
8 P M Mr A Clifford Brewer Care of Advanced Carcinoma of the Breast

Friday, 14th

University of London
5 30 P M (London School of Hygiene and Tropical Medicine) Professor Mothes Biosynthesis of Alkaloids (Second of two lectures)
Postgraduate Medical School
10 A M Mr B J Bickford Fundamental Considerations of Structure and Function in Thoracic Surgery
4 P M Prof E J Wayne Treatment of Thyroid Disease and Methods of Assessing Therapeutic Response
Institute of Neurology
5 30 P M Dr Derek Richter Biochemical Aspects of Anoxic and Hypoglycæmic States
Institute of Laryngology and Otology
5 30 P M Mr Maxwell Ellis General Principles of the Surgical Treatment of Cancer of the Larynx and Hypopharynx
Fellowship of Postgraduate Medicine
10 A M (Rheumatism Unit, St Stephen's Hospital, Fulham Road, S W 10) Prof Joseph Trueta Considerations on Degenerative Arthritis (Inaugural lecture of weekend course in the rheumatic diseases)

The Lancet · Saturday 15 March 1958

EFFECTS OF LINOLENIC AND STEARIC ACIDS ON CHOLESTEROL-INDUCED LIPOID DEPOSITION IN HUMAN AORTIC CELLS IN TISSUE-CULTURE *

DAVID D RUTSTEIN
M.D
PROFESSOR OF PREVENTIVE MEDICINE

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A CHANCE observation in our laboratory led to the study of factors affecting lipoid deposition in tissue-cultures of cells from the human aorta The effects of steroids, such as cortisone, on sodium and potassium exchange between the medium and human heart-cells in tissue-culture were under study Cholesterol, a steroid without known direct effect on sodium and potassium exchange was added to one of the control cultures After eight days' growth cells exposed to cholesterol were found to contain granules which stained with sudan IV and with Liebermann-Burchard reagents This observation led us to initiate studies on the deposition of lipoid in tissue cultures of human aortic lining in a medium containing human blood-serum

Materials and Methods

Standardised stock tissue-cultures of cells from human aorta are grown by a method originally developed in this laboratory for growing cells from fragments of human heart (Ingenito et al. 1958)

Briefly, sterile resected coarctations of the aorta ‡ are quickly transferred to the laboratory, and their inner lining is stripped off and cut into pieces about 1 mm in diameter These fragments are planted in Earle 'T-60' flasks on a plasma clot in a medium containing 40% human blood-serum, 20% chick-embryo extract$_{50}$, and 40% Hanks' balanced salt solution (Scherer et al 1955) Other constituents of the medium are 0 002% phenol red, penicillin-G 100 units, and streptomycin sulphate 50 μg per ml of medium

In all the experiments, observations are made in duplicate Two Earle 'T-15' flasks, each containing two transplants of growing aortic tissue from stock cultures in T-60 flasks, are prepared for each control and for each experimental medium. After transfer to the T-15 flasks all the cultures are incubated at 37 5° C for four days, by which time growth is usually luxuriant At this point the medium is replaced by control medium or by experimental media containing cholesterol, or fatty acid, or both

Cholesterol is added to the medium in two different ways—in ethanol solution and in aqueous solution bound to beta-lipoprotein §

The ethanol solution is prepared and added as described for other steroids (Leonard and Rutstein 1953)

Briefly, a freshly prepared solution of cholesterol (*U S P*, *Merck*) 300 mg per 100 ml in 95% ethanol is slowly diluted, with constant stirring, by the addition of Hanks' balanced salt solution to a final concentration of 1 to 15 ethanol-in-salt solution Aliquots of this solution are incorporated into the medium to final concentrations of 1–5 mg of cholesterol per 100 ml The ethanol concentration is maintained constant in all the flasks in each experiment by adding appropriate amounts of a 1 to 15 ethanol-in-salt solution to those

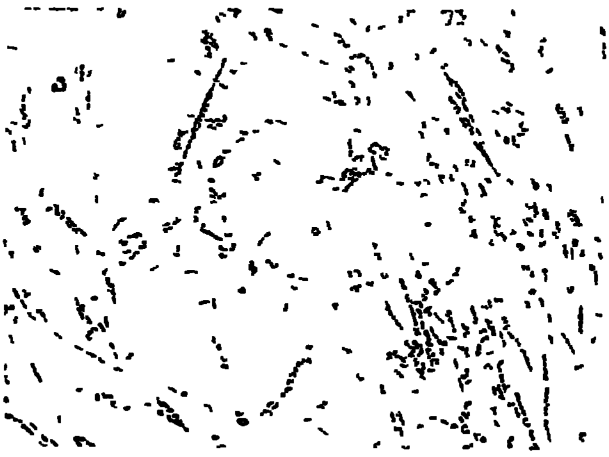

Fig 1—Control Human aortic tissue (donor M B) after five days in normal medium (serum donor T G) Figs 2-15 concern the same donors In this and subsequent illustrations (figs 2-35) the tissue was stained with sudan IV and is magnified ×130

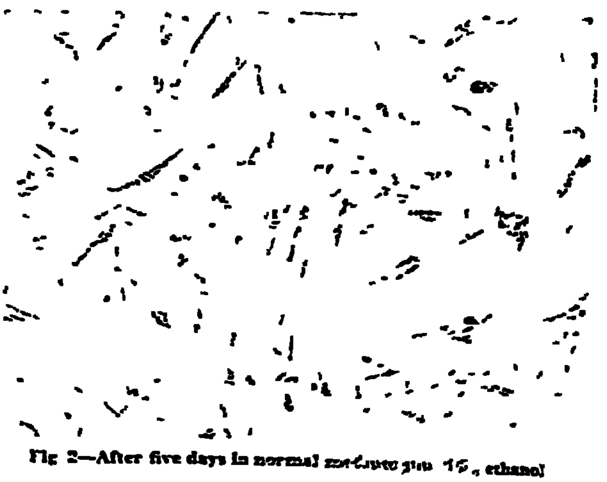

Fig 2—After five days in normal medium plus 1% ethanol

cultures in which the medium contains less than the maximum amount of cholesterol

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* This study is supported by a grant from the American Heart Association We are also indebted to M and Mme Pierre Lepaulle of Paris, France, for the Marie Laure Fund for Research in Rheumatic Fever and Related Diseases at the Harvard Medical School This Fund made possible the original research from which the present study evolved

† Lederle Research Fellow from the University of Bologna (Prof Giulio Sotgiu)

‡ Grateful acknowledgment is made to Dr Robert E. Gross, surgeon-in-chief, Children's Medical Center, Dr Dwight E Harken, surgeon and chief of the department of thoracic and cardiac surgery, Peter Bent Brigham Hospital, and Dr John Gordon Scannell, associate visiting surgeon, Massachusetts General Hospital, Boston, for a supply of resected coarctations of the aorta

§ We are indebted to Dr John Lawrence Oncley, professor of biological chemistry, Harvard University Medical School, and his staff for making available to us freshly prepared solutions of cholesterol bound to beta lipoprotein of density 1 03 (Oncley et al 1957)

Preliminary experiments show that concentrations of ethanol up to 2·5% by volume do not have any visible effect on either cell proliferation or cell morphology In all the experiments in which cholesterol was added in ethanol, the ethanol concentration never exceeded 1·75%, and in most cases it was not more than 1·4%

By the second method, cholesterol bound to beta-lipoprotein was added in concentrations of 10–70 mg of bound cholesterol per 100 ml Combining the beta-lipoprotein solution and the constituents of the medium in the cold at 4° C always yielded clear solutions

The fatty acids are added by diluting stock ethanol solutions (linolenic acid 5 g per 100 ml, stearic acid 1·25 g per 100 mls) with medium The amount of ethanol added to the medium

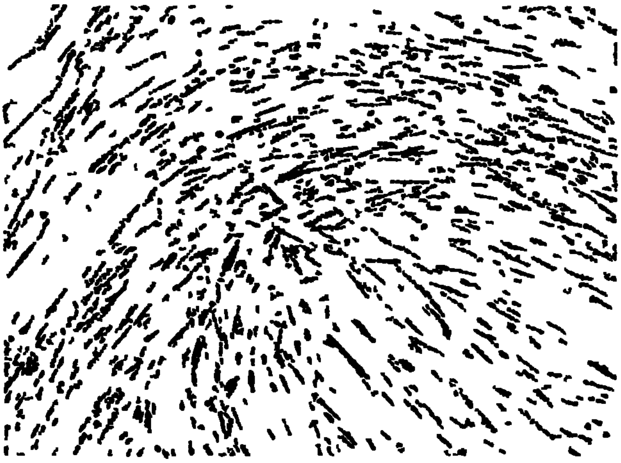
Fig 3—After five days in normal medium plus cholesterol 1 mg per 100 ml in ethanol

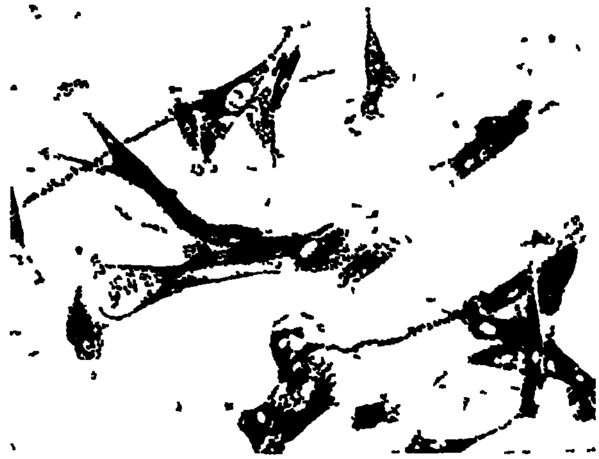
Fig 6—After five days in normal medium plus cholesterol 5 mg per 100 ml in ethanol

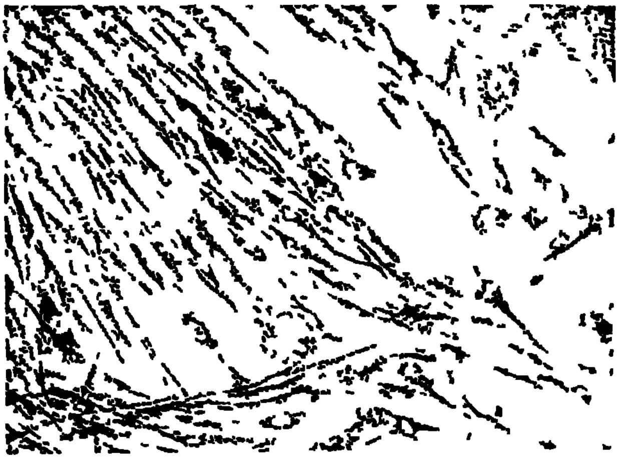
Fig 4—After five days in normal medium plus cholesterol 2 mg per 100 ml in ethanol

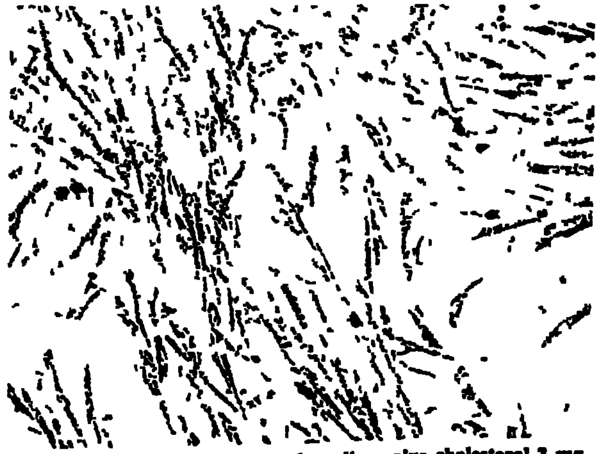
Fig 7—After five days in normal medium plus cholesterol 3 mg per 100 ml in ethanol followed by five days in normal medium

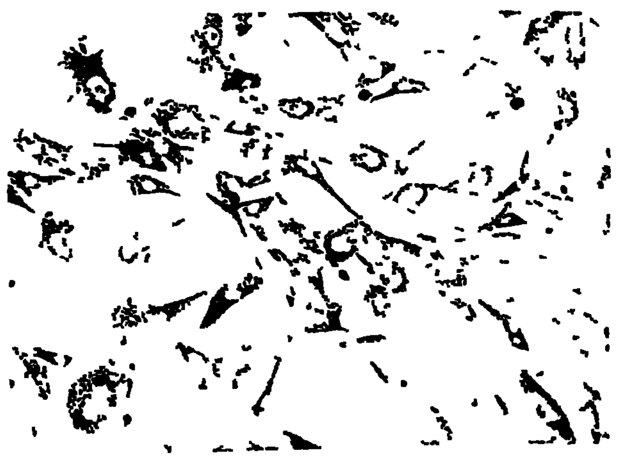
Fig 5—After five days in normal medium plus cholesterol 3 mg per 100 ml in ethanol

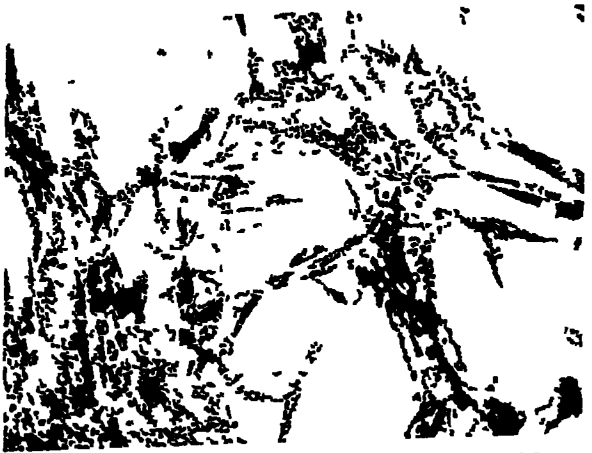
Fig 8—After five days in normal medium plus cholesterol 3 mg per 100 ml in ethanol followed by two more days in the same medium

containing the highest concentration of fatty acid is negligible—linolenic acid 0 02% and stearic acid 0 08%

The intracellular deposition of lipoid—usually first noted on the fourth or fifth day and reaching a maximum on the fift to eighth day after the experiment is begun—is confirmed b staining with sudan IV In certain experiments, as already stated, the cells are stained with Liebermann-Burchard reagents In each experiment comparisons are always made wi tissue fragments from the same stock culture in normal mediu

In the photographs as reproduced here the magnification is approximately 130

Results

Deposition of Lipoid in Tissue when Cholesterol is added in Ethanol Solution

The control culture (fig 1) and that to which 1 75% ethanol has been added—the ethanol control (fig 2)—look alike at seven days Lipoid deposition begins to

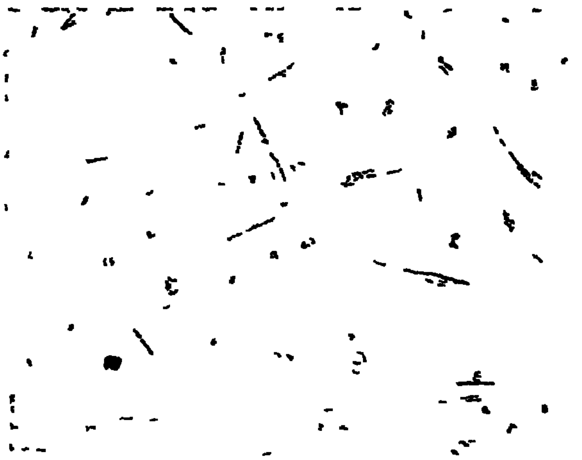

Fig 9—Control After six days in normal medium

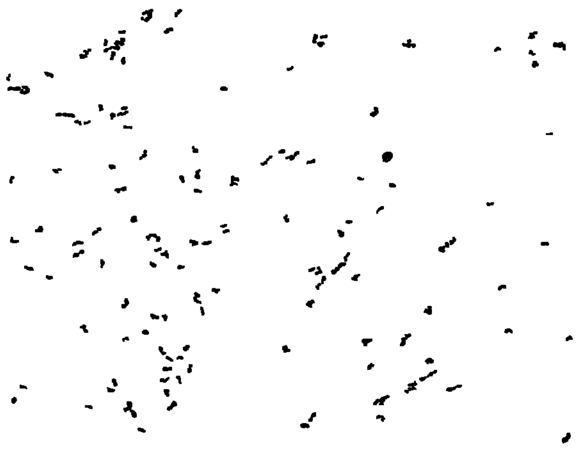

Fig 10—After six days in normal medium plus 1 5 ethanol

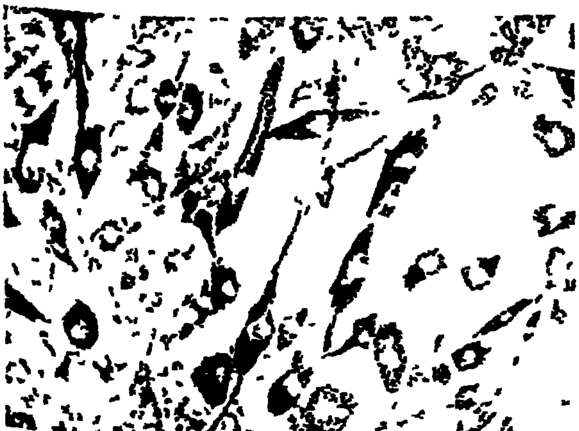

Fig 11—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol

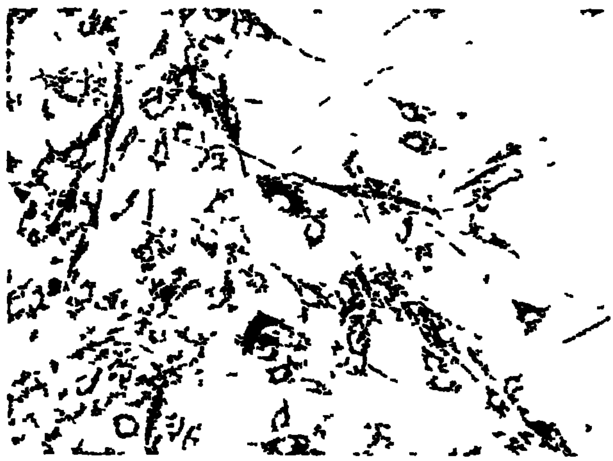

Fig 12—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol and linolenic acid 0 005 mg per 100 ml

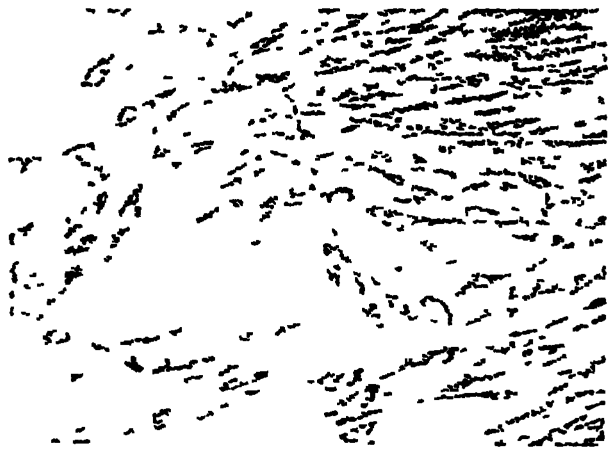

Fig 13—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol and linolenic acid 0 05 mg per 100 ml

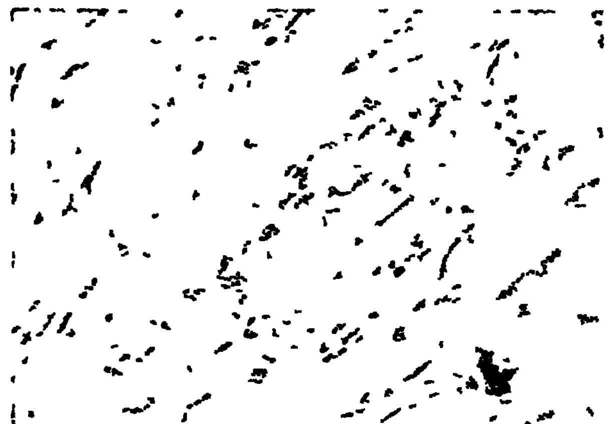

Fig 14—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol and linolenic acid 0 5 mg per 100 ml

appear when cholesterol has been added at a concentration of 1 mg per 100 ml (fig 3) and is more clearly seen at 2 mg (fig 4) At a concentration of 3 mg of added cholesterol per 100 ml, intracellular deposition of lipoid is clearly seen (fig 5) and is always associated with enlargement of the entire cell, including the nucleus These changes are even greater when the concentration of the added cholesterol is 5 mg per 100 ml (fig 6) The intracellular lipoid stains with the Liebermann Burchard reagents as well as with sudan IV When polarised light is passed through the lipoid particles, the plane of light is not rotated

When the medium containing added cholesterol 3 mg per 100 ml (fig 5) is replaced at eight days with

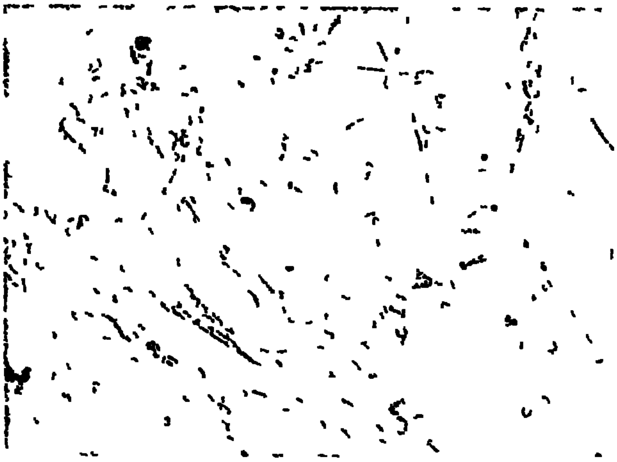

Fig 15—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol and linolenic acid 1 mg per 100 ml

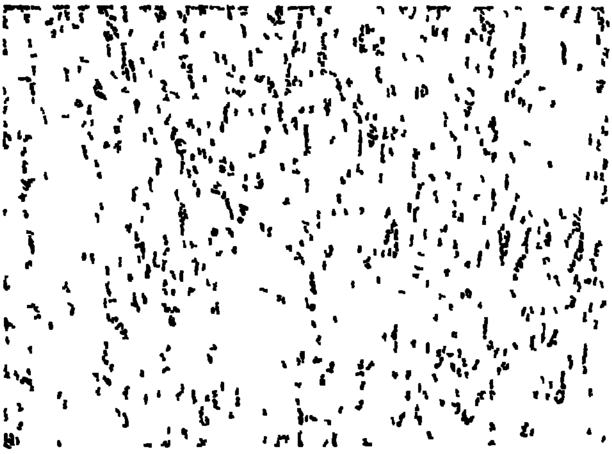

Fig 16—Control After six days in normal medium (aortic tissue donor D L, serum donor T G) The same donors apply in figs 17-22

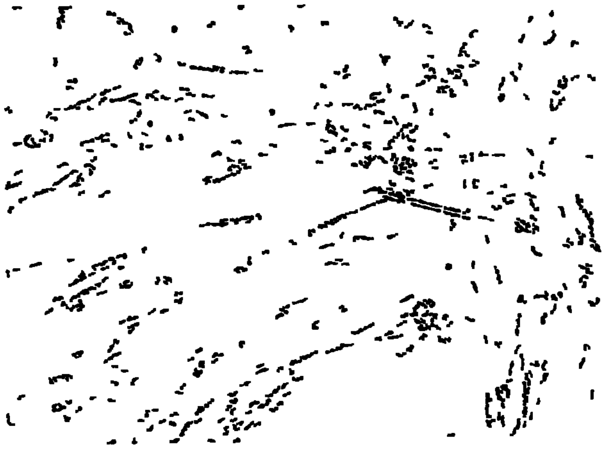

Fig 17—After six days in normal medium plus 1·5% ethanol

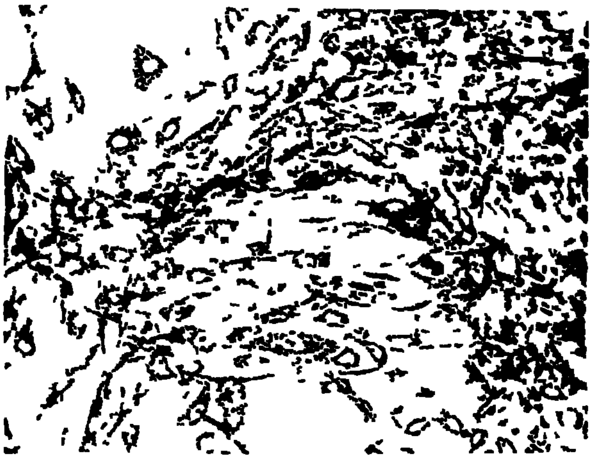

Fig 18—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol

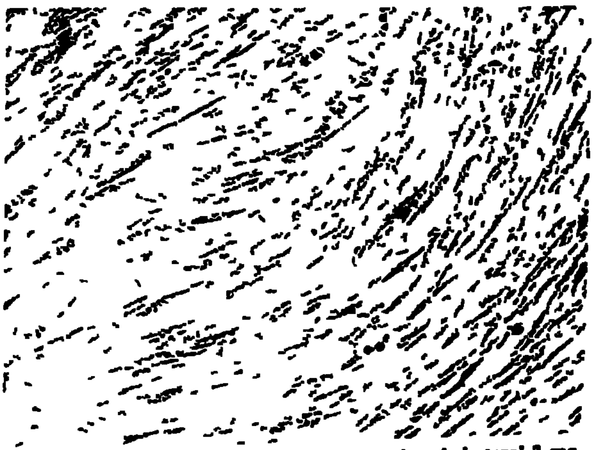

Fig 19—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol and linolenic acid 1 mg per 100 ml

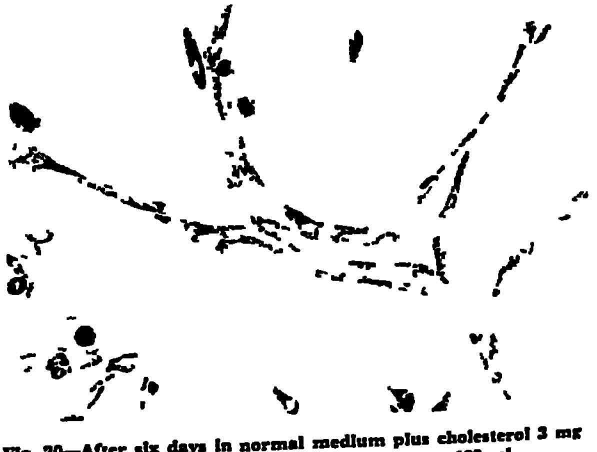

Fig 20—After six days in normal medium plus cholesterol 3 mg per 100 ml in ethanol and stearic acid 1 mg per 100 ml

normal medium, the cells gradually regain their normal appearance by the end of five more days (fig 7), but some deposited lipoid remains On the other hand, if the cultures are fed again with medium containing the same concentration (3 mg per 100 ml) of cholesterol, all the cells show increased deposition of lipoid (fig 8) and die during the next two days

Inhibition by Linolenic Acid of Tissue Lipoid Deposition when Cholesterol is added in Ethanol Solution

There are slight differences within the range of normal between the control and the ethanol control cultures (figs 9 and 10) Cultures to which cholesterol 3 mg per 100 ml has been added in ethanol show deposition of lipoid (fig 11) When increasing amounts of linolenic

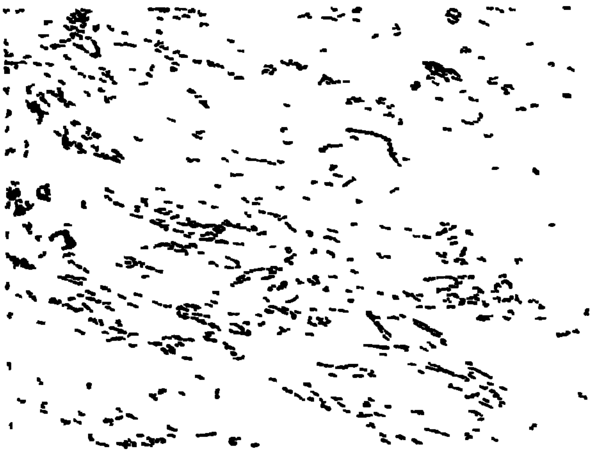

Fig 21—After six days in normal medium plus linolenic acid 1 mg per 100 ml

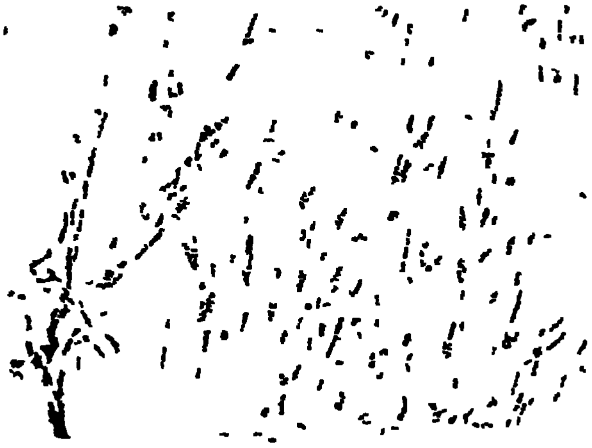

Fig 22—After six days in normal medium plus stearic acid 1 mg per 100 ml

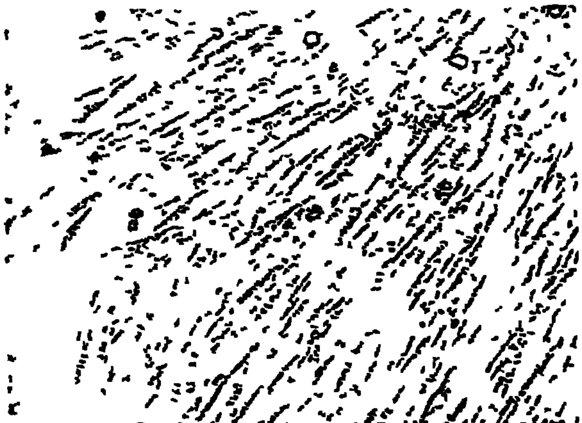

Fig 23—Control After five days in normal medium (aortic tissue donor S B., serum donor A L.) The same donors apply in figs. 24-26

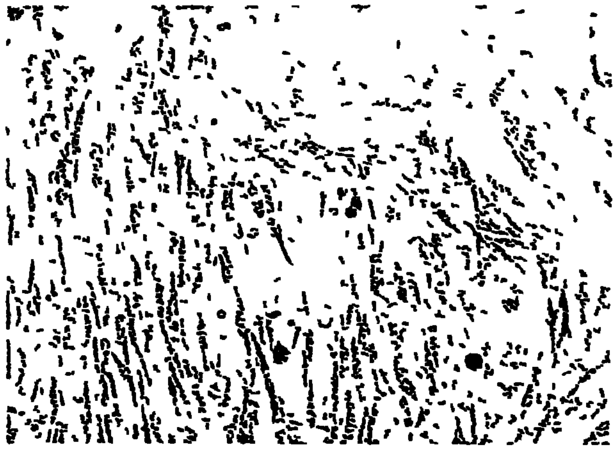

Fig 24—After five days in normal medium plus cholesterol 10 mg per 100 ml in beta-lipoprotein solution

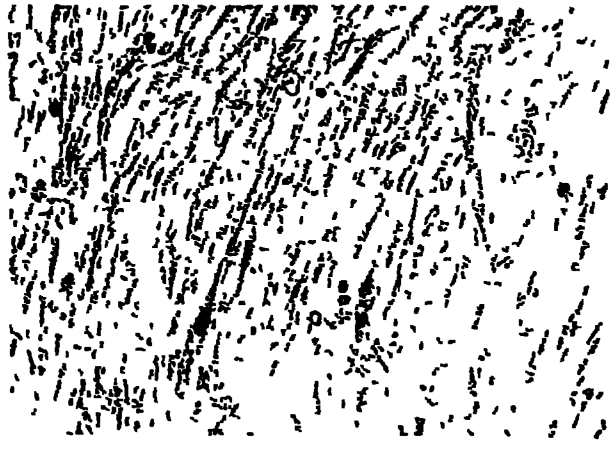

Fig 25—After five days in normal medium plus cholesterol 30 mg per 100 ml in beta-lipoprotein solution

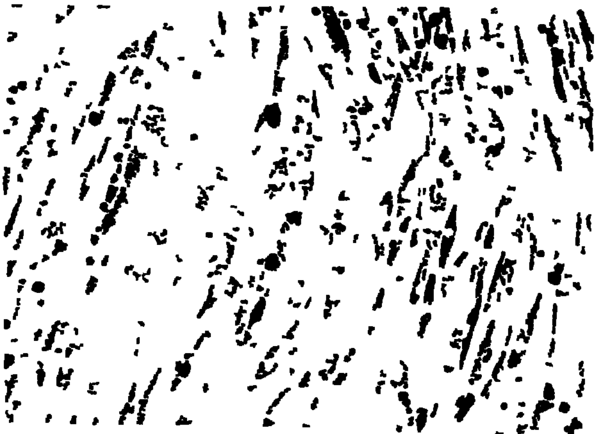

Fig 26—After five days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution

acid are added simultaneously with the cholesterol, decreasing amounts of lipoid are deposited in the cells The decrease is first evident when the concentration of added linolenic acid has been 0 005 mg per 100 ml (fig 12), and is greater when it has been 0 05 mg (fig 13) Deposition is very slight when linolenic acid has been added at a concentration of 0 5 mg per 100 ml (fig 14), and absent with a concentration of 1 mg per 100 ml (fig 15)

Inhibition by Linolenic Acid and Potentiation by Stearic Acid of Tissue Lipoid Deposition when Cholesterol is added in Ethanol Solution

The control cultures appear as before (figs 16 and 17)

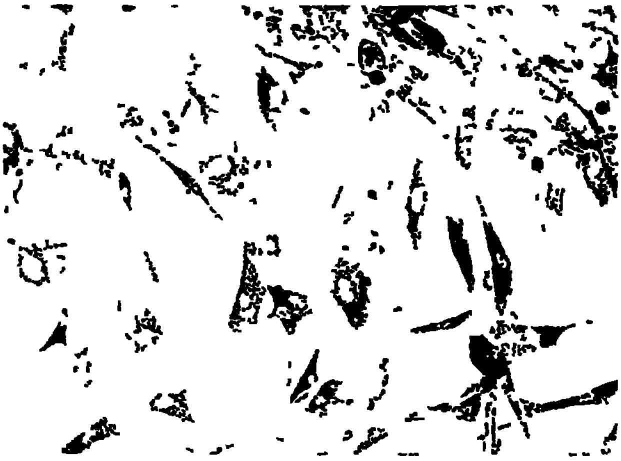

Fig 27—After five days in normal medium plus cholesterol 70 mg per 100 ml in beta-lipoprotein solution

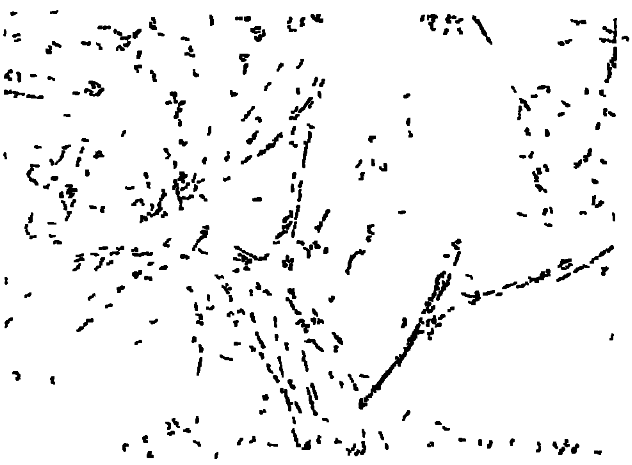

Fig 28—Control After five days in normal medium (aortic tissue donor J C, serum donor W R) The same donors apply in figs 29-31

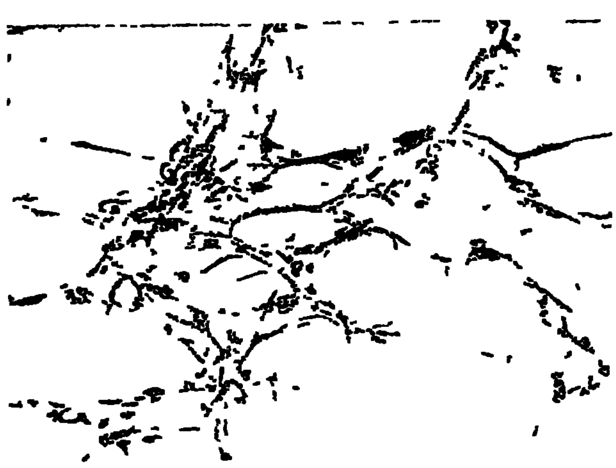

Fig 29—After five days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution

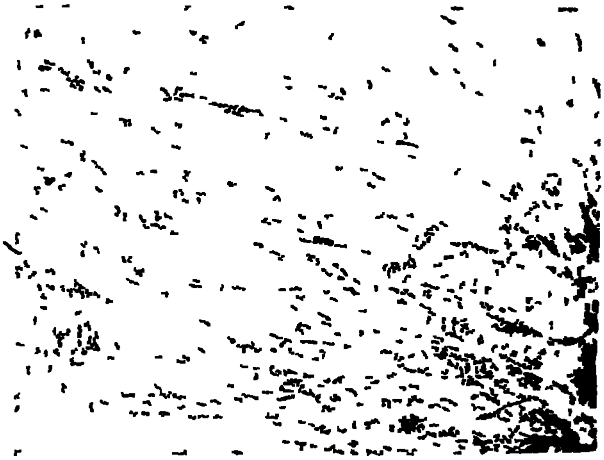

Fig 30—After five days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution followed by five days in normal medium

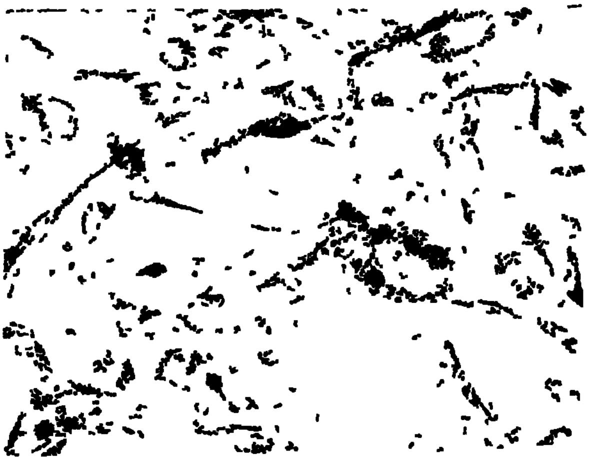

Fig 31—After five days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution followed by five more days in same solution

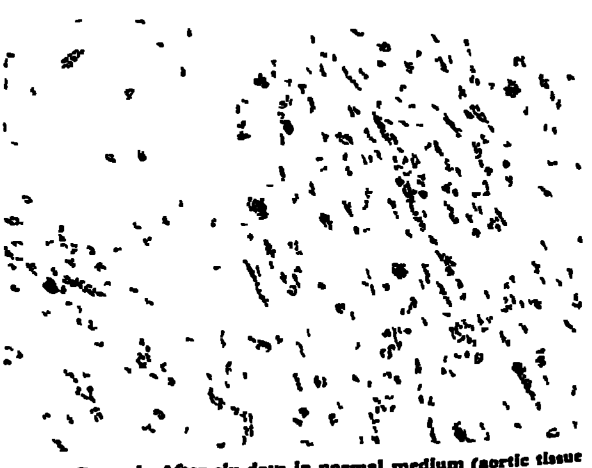

Fig 32—Control After six days in normal medium (aortic tissue donor A D, serum donor W R) The same donors apply in figs 33-35

Lipoid is deposited in the cells to which cholesterol 3 mg per 100 ml has been added in ethanol (fig 18) When linolenic acid has been added simultaneously at a concentration of 1 mg per 100 ml, the intracellular deposition of lipoid is considerably decreased (fig 19), but, when the corresponding saturated fatty acid, stearic acid, has been added in the same concentration of 1 mg per 100 ml, the lipoid deposition is increased and the cells become very large (fig 20) In control cultures, when linolenic acid has been added alone at a concentration of 1 mg per 100 ml, the culture looks like the normal control (fig 21), whereas in cultures to which stearic acid in the same concentration has been added alone the deposition of lipoid is very slightly increased (fig 22)

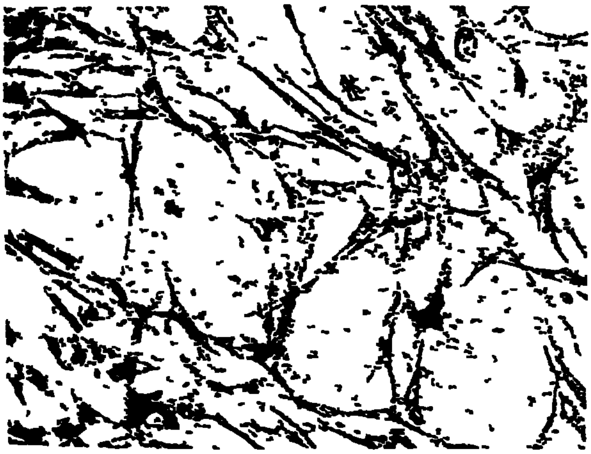

Fig 33—After six days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution.

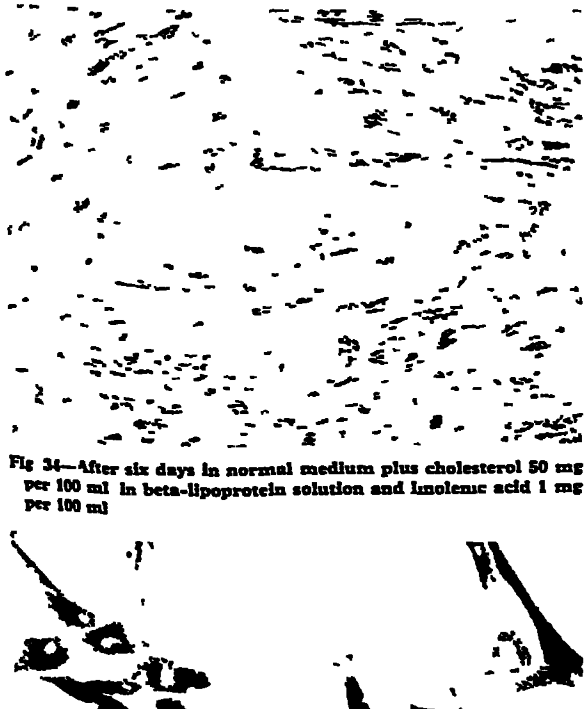

Fig 34—After six days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution and linolenic acid 1 mg per 100 ml

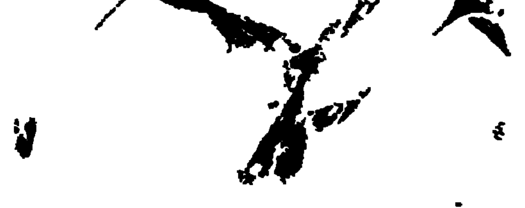

Fig 35—After six days in normal medium plus cholesterol 50 mg per 100 ml in beta-lipoprotein solution and stearic acid 1 mg per 100 ml.

Tissue Lipoid Deposition when Cholesterol bound to beta-Lipoprotein is Added

When beta-lipoprotein cholesterol is added, the intracellular deposition of lipoid is similar to that obtained by adding cholesterol in ethanol, but at a different range of concentration

The control culture (fig 23) resembles the culture containing cholesterol bound to beta-lipoprotein, at a concentration of 10 mg per 100 ml (fig 24) Intracellular lipoid deposition first appears when the concentration of added cholesterol bound to beta-lipoprotein has been 30 mg per 100 ml (fig 25)

At 50 mg per 100 ml intracellular lipoid deposition is clearly seen and is associated with an increase in the size of the cells (fig 26) At this concentration of 50 mg per 100 ml, added cholesterol bound to beta-lipoprotein produces about as much intracellular lipoid deposition as does added cholesterol in ethanol in a concentration of 3 mg per 100 ml When beta-lipoprotein cholesterol has been added in a concentration of 70 mg per 100 ml, the deposition is even greater (fig 27)

Reversibility of Tissue Lipoid Deposition Previously Induced by Cholesterol bound to beta-Lipoprotein

The control culture appears as before (fig 28) The intracellular deposition of lipoid induced by added beta-lipoprotein cholesterol at a concentration of 50 mg per 100 ml (fig 29) is reversible When such medium is replaced at five days with normal medium, the lipoid deposited in the cells almost all disappears by the end of five more days (fig 30) In contrast, if the culture is fed again with medium containing added beta-lipoprotein cholesterol in the same concentration of 50 mg per 100 ml, the lipoid deposited in the cells persists (fig 31)

Inhibition by Linolenic Acid and Potentiation by Stearic Acid of Tissue Lipoid Deposition when Cholesterol is added bound to beta-Lipoprotein

The control culture appears as before (fig 32) When the beta-lipoprotein cholesterol has been added in a concentration of 50 mg per 100 ml, lipoid is deposited in the cells (fig 33) When linolenic acid 1 mg per 100 ml has been added simultaneously, then intracellular deposition of lipoid is almost completely inhibited (fig 34) In contrast, when a similar concentration of stearic acid has been added with beta-lipoprotein cholesterol 50 mg per 100 ml, much more lipoid is deposited in the cells, which become much larger (fig 35)

Further Experiments

Each of the steps in the above experiments has been performed from three to seven times with similar results The morphological changes reported here are being investigated by chemical methods

This technique makes possible the testing, at the level of intracellular lipoid deposition, of hypothetical mechanisms of human atherosclerosis, whether based on epidemiological evidence or on abnormally high levels of lipoid constituents of human blood-serum The technique is now being applied to the study of human atherosclerosis

Summary and Conclusions

Factors affecting the intracellular deposition of lipoid can be studied in human aortic cells in tissue-culture in a medium containing human blood-serum

When cholesterol in ethanol is added to the culture medium, the amount of lipoid deposited in the cells is proportional to the amount of cholesterol added

1 At a concentration of 1 mg of added cholesterol per 100 ml, there is very little evidence of intracellular lipoid deposition

2 At a concentration of 3 mg per 100 ml, intracellular lipoid deposition regularly appears and is associated with an increase in the size of the cells

3 At a concentration of 5 mg per 100 ml, intracellular lipoid deposition is considerable and the cells are enormously increased in size

Similarly, when cholesterol bound to beta-lipoprotein is added to the culture medium, the amount of lipoid deposited in the cells is proportional to the amount of cholesterol added

1 At a concentration of 30 mg of added cholesterol per 100 ml, there is very little evidence of intracellular lipoid deposition

2 At a concentration of 50 mg per 100 ml, intracellular lipoid deposition regularly appears and is associated with an increase in the size of the cells

3 At a concentration of 70 mg per 100 ml, intracellular lipoid deposition is considerable and the cells are enormously increased in size

The intracellular deposition caused by adding cholesterol (whether in ethanol or protein-bound) disappears in five days if the medium containing the cholesterol is replaced by normal medium

The intracellular deposition caused by adding cholesterol (whether in ethanol or protein-bound) is completely inhibited by simultaneous addition of linolenic acid (1 mg per 100 ml) It is increased by simultaneous addition of stearic acid (1 mg per 100 ml)

Thus, in tissue cultures of human aortic cells, deposition of lipoid can be induced by cholesterol, is reversible, can be inhibited by an unsaturated fatty acid (linolenic acid), and can be potentiated by the corresponding saturated fatty acid (stearic acid)

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"However impressive the difference between the hand of a cultured person and that of a prehistoric or primitive man may be externally, there can be no question of any fundamental difference Primitive man also works, touches, recognises and shapes objects, expresses his feelings, thoughts and desires with the help of the hand If he did not do this he would not be a man As the ape is not in a position to carry out these activities or to do so only in a very modest degree, his hand remains an organ of grasping, regardless of the degree of dexterity and mobility with which it is equipped and of the sort of movements which, through natural endowment, exercise and training, it may be capable Between an organ of grasping and an expressive hand there is a large gap, which man alone has succeeded in bridging"—Prof GÉZA RÉVÉSZ *The Human Hand* Translated by John Cohen *London*, 1958

THE ÆTIOLOGY, INCIDENCE, AND HEREDITY OF PRE-ECLAMPTI TOXÆMIA OF PREGNANCY

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THE first difficulty which the student of this su
encounters is one of nomenclature The term to
is unsuitable for a disorder which has never been p
to be due to any kind of poisoning, the term pre-ecla
should, strictly speaking, be applied only to patients
later develop eclamptic convulsions, and nowadays
a very small minority ever do so Specific hyperte
disease of pregnancy is also an unsuitable title, be
it seems clear that some patients develop œdema
albuminuria late in pregnancy without hyperten
and in any case it is impossible to fix an arbitrary
above which hypertension may be said to be pre
We therefore reluctantly use the term pre-eclan
toxæmia (sometimes abbreviated to toxæmia), becau
is current

The next difficulty is to define what is and is not
eclamptic toxæmia and to differentiate it from hy
tension accompanying and complicating pregna
This difficulty we have tried to overcome in va
ways, which will be specified We are impressed by
mildness of the symptoms and signs in many cases
being diagnosed, it is clear that many would have
missed altogether in patients who had not had pr
antenatal care

Possibility of Antigenic Incompatibility between Mother and Fœtus as a Cause of Pre-eclamptic Toxæ

No satisfactory hypothesis for the causation
mechanism of pre-eclamptic toxæmia has yet been
forward, and we do not propose to review the vast lit
ture which always accumulates on any subject about wh
the medical profession is particularly ignorant T
object of this study is to seek evidence as to whet
pregnancy toxæmia may be due to antigenic inco
patibility between mother and fœtus

Let it be supposed that the mother has a protein
other potential antigen represented by the gene E, wh
is not present in the fœtus, whose constitution, so
as this allele is concerned, is that of the homozygote
Clearly the mother must be heterozygous (Ee) becau
if she were homozygous (EE) she could not have a fœ
who was homozygous ee Some of her potentially an
genic protein passes into the fœtus, who manufactu
an antibody to it, which in turn is absorbed by
mother and damages the mother's kidneys, the conditi
being akin to rhesus incompatibility in reverse

Such an explanation is attractive for the follow
reasons

(1) It would explain why pregnancy toxæmia never ta
place until the later months of pregnancy

(2) It would explain the rapid recovery of the great major
of patients soon after the pregnancy is terminated, whet
naturally or artificially

(3) It would explain the fact that a woman may have toxæmia in some pregnancies but not in others, and that a woman who has had pre-eclamptic toxæmia is more liable than the general population to have it in a subsequent pregnancy

(4) It would explain the increased incidence of pre-eclamptic toxæmia in twin pregnancies For if the twins are identical a double dose of antibody may be produced, while if they are dissimilar there is twice the normal chance that one of them may be homozygous ee

(5) It would explain why the fœtus does not have either albuminuria or kidney disease

The hydatidiform mole might be, as Kalmus (1946) suggests, a case in which incompatibility worked both ways, the fœtus as well as the mother being adversely affected

The theory of antigenic incompatibility as a cause of pregnancy toxæmia was put forward by Platt (1947), who was then unaware of the papers of Penrose (1946) and Kalmus (1946) Kalmus postulated the reverse situation—that the mother might be the homozygote and the fœtus the heterozygote This seems to us to be less likely It should be noted that, whereas an analogy may be drawn between this situation and rhesus incompatibility leading to erythroblastosis, we do not suggest that the condition has necessarily anything to do with blood-groups which are at present recognised or which may be discovered in the future

If only one pair of genes, E and e, is commonly involved in the causation of pregnancy toxæmia in this country, the hypothesis can be examined by studying the incidence of pre-eclampsia in the relatives of women who have suffered from the disorder The simplest case will be clear at a glance if a woman, who for the sake of clarity we will call the proposita, has pre-eclamptic toxæmia, her mother could not have had pre-eclamptic toxæmia during the pregnancy in which the proposita was the fœtus For the proposita must be Ee and, no matter what her mother's genetic constitution regarding this gene, the toxæmic configuration (Kalmus' term)—Ee/ee—cannot have existed Similarly, a daughter (ee) arising from a toxæmic pregnancy cannot herself later have toxæmia If, therefore, it can be shown that the mothers of toxæmic women never had pre-eclamptic toxæmia in the relevant pregnancies, and also that daughters arising from toxæmia pregnancies never have toxæmia in their own pregnancies, this evidence would go a long way towards supporting the hypothesis of antigenic incompatibility

Furthermore, if the gene frequencies of E and e in the population can be calculated, the likelihood of various relatives of the proposita having pre-eclamptic toxæmia can also be calculated, and it will be seen from tables I and v that some of these relatives will be more, and others less, likely to have pre-eclamptic toxæmia than will the general population of women exposed to the risk of pregnancy

If, however, there are several fairly common potential causes of antigenic incompatibility (which we might call factors E, F, and G), it is unlikely that statistical proof will be forthcoming, and the hypothesis must wait until more objective proofs of incompatibility are available We are thus in the happy position of being perhaps able to bring evidence in favour of our explanation but being quite incapable of disproving it In fact, the pilot trial here described does not bring to light any strong evidence in favour of the antigenic theory

TABLE I—INCIDENCE OF PRE-ECLAMPTIC TOXÆMIA IN PROPOSITÆ AND THEIR RELATIVES ON THE ASSUMPTION OF AN ANTIGENIC INCOMPATIBILITY BETWEEN MOTHER (Ee) AND FŒTUS (ee)

Gene frequencies of E and e are p and q respectively, where $p+q=1$ (after Kalmus)

General incidence in the population	pq^2
Incidence in mother of proposita (proposita being fœtus)	0
" " " (in another pregnancy)	$\frac{1}{4}q$
" sisters of propositæ	$\frac{1}{4}q(1-pq)$
" wives of brothers of propositæ	$\frac{1}{4}pq(1+2q)$
" mothers-in-law (husband being fœtus)	pq
" " " (in another pregnancy)	$\frac{1}{4}pq(2+q)$
" husband's sisters	$\frac{1}{4}pq(1-2q)$
" husband's brothers' wives	$\frac{1}{4}pq(1+3q)$
" proposita in another pregnancy (having had a toxæmic one)	$\frac{1}{4}(1-q)$

Table I, which has been compiled with the help of Dr Kalmus, shows the relative frequency of pregnancy toxæmia in the general population and in relatives of toxæmic women, assuming a frequency for genes E and e of p and q respectively The next step—the calculation of gene frequencies—depends on the ascertainment of the incidence of pre-eclamptic toxæmia in the general population

General Incidence of Pre-eclamptic Toxæmia

Of the incidence of toxæmia in the general population surprisingly little is known Most of the existing records are from highly selected hospital populations The only papers known to us which attempt to avoid this bias are that by Gemmell, Logan, and Benjamin (1954), and the obstetric survey of the South West faculty of the College of General Practitioners (1957)

Gemmell et al estimated the number of cases of pre-eclamptic toxæmia in Liverpool in 1951, on the assumption that all such cases would be sent to a hospital or other maternity unit They compared this figure with the total number of births in Liverpool in the same year There are obviously some potential fallacies in their method, and these workers admit that they could not separate cases of hypertension complicating pregnancy from cases of pre-eclamptic toxæmia Like other students of this subject, they find that pre-eclamptic toxæmia is commoner in first pregnancies (8 5%) than in subsequent pregnancies (4 2%) They estimate the total chance of any parous woman developing pre-eclamptic toxæmia at some time during her childbearing life at about 13%

The obstetric survey from the College of General Practitioners (1957) also does not distinguish between pre-existing hypertension and pregnancy toxæmia It records an incidence of hypertension (140/90 or more) in 16% of primiparæ and 9% of multiparæ Of these hypertensives, 43% of primiparæ and 31% of multiparæ also had albuminuria—i.e, 7% and 3% approximately of total pregnancies The interesting comment is made that of these hypertensive albuminuric cases only 38% of primiparæ and 30% of multiparæ were delivered in specialist hospitals It is not stated how many were delivered at home, and the usual practice in this respect may be very different in the South West of England from that which would obtain in a city like Liverpool, but the survey suggests that the method of Gemmell et al (1954) may miss some home deliveries of pre-eclamptic patients

In an attempt to make our own estimate of the incidence of toxæmia in an unselected population, we sent a questionary to the 716 men and women who graduated in medicine in Manchester University in 1946–55 We admit of course that this series is not unselected so far as intelligence and social class are concerned, but we know of no evidence that pregnancy toxæmia is determined by such factors The group is also selected as regards age, but it seemed to us that women doctors who have themselves had babies, and male doctors whose wives have had babies, should be the most reliable witnesses possible as to whether pregnancy toxæmia had occurred or not

TABLE II—FATE OF QUESTIONARIES

No of graduates in medicine 1946–55	716
No untraceable (letters returned by Post Office)	25
No written-off (see text)	6
No of intermarriages known	36
No of unmarried siblings deleted (see text)	4
No not replied after 2nd letter	72*
No of replies analysed	573
Total	716

*Some of these may be women known to us by their maiden name whose husbands have replied

The questionary asked whether the "wife" (i e, either the woman doctor or the doctor's wife) had had pregnancies, if so, how many and whether they were complicated by toxæmia, and if so, whether hypertension, œdema, and albuminuria were present or only some of these phenomena The witnesses were asked similar questions about pregnancies of the wife's mother, her sisters, her brother's wives, her mother-in-law, her husband's sisters, and her husband's brothers' wives

Table II shows that, of 716 questionaries, only 573 are available for analysis In 36 instances this is due to intermarriage between graduates, clearly in such cases husband and wife can only give the same information † Again, when unmarried graduate siblings exist, they can give no additional information about their families, but in the case of married siblings—e g, two brothers, both married and having families, and both graduates—both have been included, even though this leads to a very minor degree of duplication of some of the data Cases described as written-off include several people who were of African or Asiatic race, or who were adopted children, and could give no information of value Half-brothers and half-sisters, of whom there were very few, were not counted as brothers and sisters Abortions, and pregnancies still unfinished at the time of completing the questionary, were not counted as pregnancies

Table III shows the incidence of pregnancy in the "wives" of the series This is the table which should give the most accurate information, because these pregnancies, nearly all of which occurred within the last ten years, will have been most carefully observed It will be seen that altogether 290 "wives" were at risk in the sense of having had at least one pregnancy, and among these the incidence of toxæmia in the first pregnancy is 11 7%, but this may be somewhat exaggerated, and here we come at once into one of the difficulties of the subject, because of the 34 cases of toxæmia occurring in first pregnancies no albuminuria was reported in 16 On the other hand, 11 of these 16 women had both œdema and hypertension (a rise of blood-pressure significantly above that observed earlier in the pregnancy) so it seems reasonable to estimate the incidence of toxæmia as 29 cases (10%) This figure is, as one would expect, somewhat higher than that of Gemmell et al (1954) and that from the College of General Practitioners (1957) The number of women having toxæmia in second pregnancies is 4% This might be a false figure if women having had one toxæmia pregnancy showed a strong reluctance to embark on a second pregnancy Such, however, was not the case Of 290 women who had had first pregnancies 153 (53%) had had second pregnancies Of 34 women who had had toxæmic first pregnancies 15 (44%) have already had second pregnancies

TABLE III—WOMAN GRADUATE OR WIFE OF GRADUATE

No of 1st pregnancies	290	Toxæmic	34*	(11 7%*)
,, ,, 2nd ,,	153	,,	8*	(5 2%*)
,, ,, 3rd ,,	39	,,	1	(2 6%)
,, ,, 4th ,,	8	,,	1	(12 5%)
,, ,, 5th ,,	2	,,	0	
,, ,, 6th ,,	1	,,	0	

*Reduced to 29 (10 0%) and 6 (4 0%) respectively (see text)
Number toxæmic only in 2nd or later pregnancy = 3
Total wives having toxæmia (corrected) = 32 (11%)

We see from table I that the general incidence of pre-eclamptic toxæmia in women exposed to the risk of pregnancy should be pq^2, where p is the gene frequency of E, and q the gene frequency of e $(p + q = 1)$, *assuming that all women in whom this maternal and fœtal incompatibility exists will develop signs of toxæmia* All observers have found toxæmia to be more common in first pregnancies than in subsequent pregnancies, therefore one must assume that there is some factor which protects the mother in subsequent pregnancies, and we will take the incidence in *first pregnancies* as our basis for the calculation of gene frequencies If pq^2 equals 10% or 0 1, there are two figures which we may take for the approximate values of p and q—either p = 0 59, q = 0 41 or p = 0 13, q = 0 87 ‡

TABLE IV—RELATIVES OF WOMEN GRADUATES OR OF MEN GRADUATES' WIVES

Mothers		
1st pregnancies	458*	
Pregnancy history unknown	14	
	444	
Toxæmia in 1st pregnancy		15 (3 4%)
,, ,, subsequent pregnancy only		9 (2·0%)
Total		5 4%
Sisters		
1st pregnancies	*167*	
Toxæmia in 1st pregnancy		10 (6·0%)
,, ,, subsequent pregnancy only		3 (1 8%)
Total		7 8%
Wives of brothers		
1st pregnancies	124	
Toxæmia in 1st pregnancy		11 (8 9%)
,, ,, subsequent pregnancy only		5 (4·0%)
Total		12 9%
Husbands' mothers		
1st pregnancies	516*	
Pregnancy history unknown	9	
	507	
Toxæmia in 1st pregnancy		17 (3 3%)
,, ,, subsequent pregnancy only		8 (1 5%)
		4 8%
Husbands' sisters		
1st pregnancies	182	
Toxæmia in 1st pregnancy		10 (5 5%)
,, ,, subsequent pregnancy only		5 (2 7%)
Total		8 2%
Husbands' brothers wives		
1st pregnancies	178	
Toxæmia in 1st pregnancy		13 (7 3%)
,, ,, subsequent pregnancy only		4 (2 2%)
Total		9 5%

*These figures are less than 573 because of the unmarried members of the series

Incidence of Toxæmia in Relatives of Toxæmic Women

Table IV shows the observed incidence of toxæmia in relatives of all the "wives" (i e, not merely the toxæmic ones), and, before analysing these more carefully, it can be seen at first glance that relatives of the same generation (i e, sisters, brothers' wives, sisters-in-law, and wives of brothers-in-law) have an incidence of toxæmia which approaches that of the "wives" themselves, whereas members of the previous generation (i e, mothers and mothers-in-law) have a considerably lower incidence This we feel is much more likely to be due to failure of diagnosis through lack of antenatal

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† The role of this Medical School as a matrimonial agency is an interesting side-issue of this inquiry

‡ Note that theoretically the greatest possible value of pq^2 is 14 81% when p = 0 33 (Kalmus 1946)

TABLE V—INCIDENCE OF TOXÆMIA IN 1ST PREGNANCIES OF RELATIVES OF TOXÆMIC WOMEN

—	Expected incidence * (see table I)		Graduate series		Portsmouth series		Manchester series		Manchester and Portsmouth series	
	If q = 0·41 %	If q = 0·87 %	Incidence	Total at risk	Incidence	Total at risk	Incidence	Total at risk	Incidence	Total at risk
General population	10	10	29	290						
Mother (proposita being fœtus)	0	0	0	48	2	38	1	38	3	76
Mother (another child)	10	22	1 (25%)	4	2 (20%)	10†	0	6†	2	16†
Mother-in-law (husband being fœtus)	24	11	4 (7%)	55	0	36	1 (3%)	30	1 (2%)	66
Mother-in-law (another child)	15	8	1 (17%)	6	0	2†	0	1†	0	3†
Sister	13	24	2 (9%)	23	11 (28%)	40	4 (9%)	46	15 (17%)	86
Brother's wife	11	8	4 (17%)	24	1 (3%)	32	1 (3%)	31	2 (3%)	63
Husband's sister	11	8	5 (14%)	35	3 (6%)	48	0	25	3 (4%)	73
Husband's brothers' wife	13	10	3 (10%)	31	0	21	0	26	0	47
Proposita herself in 1st pregnancy (subsequent pregnancy being toxæmic)	35	47	17 (53%)	32						

* On the assumption that toxæmia develops in all cases where the genetic situation allows it to.
† Some of these figures are very small because the birth order was not ascertained.
In the Portsmouth series there are 2 pairs of sisters in which both are counted as propositæ.

care than to any factor causing an increased incidence of toxæmia in the present generation.

Table V sets out the incidence of toxæmia expected in relatives of women who have actually had toxæmia themselves, based on a value for q of 0·41 or of 0·87, and calculated from table I. It will be seen that, in either case, the incidence of toxæmia in the mother of a toxæmic woman should be 0 in the relevant pregnancy, as we have already remarked. If q=0·87, the incidence of toxæmia in the mother's other pregnancies should be high, as should be the incidence of toxæmia in the sisters of toxæmic women. If q=0·41, the incidence of toxæmia in the mothers-in-law of toxæmic women during the birth of the toxæmic woman's husband should be high, and with either gene frequency the chances of toxæmia occurring again in a subsequent pregnancy are very high indeed.

Table V gives the actual incidence of toxæmia in the relatives of all women in the graduate series who have had toxæmia themselves. If the "wives", their sisters, and their husbands' sisters are included, there are altogether 54 women who have had toxæmia and whose mother's history as regards toxæmia is known and recorded. Of these 54, 3 had mothers who were also affected by toxæmia,* and in none of these 3 cases was the mother affected during the pregnancy from which the toxæmic daughter was born.

Conversely, there are 12 parous women of the present generation whose mothers had toxæmia when they were born, and in no case have these 12 daughters had toxæmia in their own pregnancies. There is thus no exception to the rule we have stated, but the figures are too small for the finding to be significant. The prediction, that the chances of pre-eclamptic toxæmia occurring again in a subsequent pregnancy are high, is of course amply justified by this table, as we would have expected from what is already known. The figures for the incidence of pregnancy toxæmia in other relatives are probably not significantly different from the normal range.

To put the hypothesis further to the test we have taken family histories from 100 women in hospital or in antenatal clinics who have had pre-eclamptic toxæmia. 50 of these were examined by A. S. and are called the Portsmouth series, and 50 were examined by R. P. and are called the Manchester series. In this part of the work we felt that selection was desirable, provided women were not selected simply because they had an interesting family history. We therefore decided in advance on the examination of a consecutive series who should fulfil the following criteria:

(1) There must be antenatal records showing clearly that the blood-pressure had remained normal and the urine free from albumin in the earlier stages of the pregnancy.

(2) The women must have later developed albuminuria and either œdema or hypertension or both. Hypertension was not strictly defined but was taken to mean rises of blood-pressure significantly above those recorded earlier in the pregnancy. In most cases there was a clear and fairly sudden onset of these signs.

Naturally *the ascertainment of family histories from* patients in this way is full of difficulties, and the data may not be very accurate. In the Portsmouth series are two pairs of sisters—i.e., each of the sisters had pregnancy toxæmia and has been counted in the series. Table V shows the incidence of pregnancy toxæmia, so far as we could ascertain it, in the first pregnancies of the relatives of these patients. We do not think there is very much that is significant in this table except that the incidence of toxæmia in the sisters of toxæmic women appears to be very high, and there are 3 cases in which the mother had pregnancy toxæmia in the pregnancy from which the proposita arose—in other words, there are 3 cases which count clearly against our hypothesis in its simplest form.

(1) One of these is not very impressive, in that the mother simply said that she had kidney trouble with her pregnancy.

(2) The second said that she had kidney trouble with both pregnancies and had much œdema.

(3) The third, an intelligent woman in the Manchester series, said that her mother had "albumin" badly when she was born and again in her other pregnancies, and in the pregnancy from which the proposita was born the mother had to rest and was taken to hospital; she had a high blood-pressure with each pregnancy.

Within the limitations of this kind of inquiry this seems to be evidence which we are bound to accept, and we therefore did not extend the series any further.

In accepting even a single case in which the daughter from a toxæmic pregnancy has toxæmia in one of her own pregnancies we have to discard the simple hypothesis proposed above. It is nevertheless possible that some more complex system of antigenic incompatibility may underlie this condition, and, if so, it would be expected to cause an irregular incidence of toxæmia among the relatives of toxæmic women, just as the simple theory would—some relationships showing an incidence raised above that in the general population, and others depressed below it We have therefore examined our data for evidence that differences in observed frequency are greater than might be expected to arise by pure chance There is some slight indication that this may be so

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* Not all of these pregnancies are recorded in table V, which shows only first pregnancies.

We have considered the incidence of toxæmia in first pregnancies of sisters of propositæ, brothers' wives, husbands' sisters, and husbands' brothers' wives To obtain adequate numbers for statistical treatment the Manchester, Portsmouth, and graduate series were combined, and where there is any duplication among subjects, as with the two pairs of sisters mentioned previously in the Portsmouth series, only one individual has been counted The result of the analysis is χ^2 8 23, $n=3p=0$ 040

A slightly more significant result is obtained if we consider also the mothers of propositæ and of their husbands both in the pregnancies when the proposita or her husband was the fœtus and in other pregnancies These cases correspond to rows 1–4 of table v, but to obtain adequate number we have had to consider all pregnancies whose histories we could obtain, not merely the first, and also to combine "mother (proposita being fœtus)" with "mother-in-law (husband being fœtus)" It happens that the frequency of toxæmia was about the same in these two classes, so no variability is obscured by combining them This group of mothers and mothers-in-law cannot, of course, be compared directly with the groups of sisters and sisters-in-law of propositæ, first because we believe the probability of diagnosis to be much smaller in the elder generation, and secondly because we have considered all their pregnancies and not only the first Considered separately the group of mothers and mother-in-law give $\chi^2=3$ 97, $n=2$, and combining for the two groups we have $\chi^2=12$ 20, $n=5$, $P=0$ 032

In the course of the inquiry we came across three histories which seem to be of interest

(1) In one case a husband's first wife died of eclampsia in her only pregnancy his second wife had toxæmia in each of two pregnancies (2) In another case the husband's brother's wife had toxæmia, but she had been married before and had no toxæmia in two pregnancies from her first husband (3) A third woman had two normal pregnancies and then changed her husband and had toxæmia in her third pregnancy

ABO and Rh blood-groups were recorded in 97 of these 100 cases Their distribution does not appear to differ significantly from that in the general population Although they are irrelevant to our paper, we record them in table VI

TABLE VI—BLOOD-GROUPS OF 97 TOXÆMIC WOMEN

O	A	B	AB	Rh+	Rh−
39	44	10	4	78	19

Summary and Conclusions

This investigation was designed to test the hypothesis that antigenic incompatibility between mother and fœtus is the cause of pregnancy toxæmia This hypothesis would explain many of the peculiar features of this condition

If a single antigenic factor were at work, evidence in favour of the hypothesis could be obtained by investigating the incidence of toxæmia in the relatives of toxæmic women

The result of this investigation strongly suggests that if incompatibility exists it is not due to a single factor, but does not rule out the possibility that several factors may be at work

In the course of the investigation we studied the general incidence of toxæmia in 573 women medical gaduates and wives of medical graduates, and their relatives

We have pleasure in acknowleding our thanks to Dr H Kalmus,, to Dr T E Roberts the medical officer of health of Portsmouth and his health visitors, to Prof W I C Morris and other members of the staff of Saint Mary's Hospitals, Manchester, and to Mrs M. Winterbottom, who did most of the work connected with the questionary

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ACCIDENTAL HYPOTHERMIA

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The body temperature in mammals is controlled by the hypothalamus, which contains separate centres for heat loss and conservation The heat-conservation centre lies in the posterior hypothalamus and is activated by stimuli from cold receptors in the skin and by fall in temperature of the blood perfusing it Efferent stimuli cause cutaneous vasoconstriction, increased muscle-tone, and shivering, and both vascular and muscular responses are potentiated by adrenaline release In extreme cold the mechanism may be inadequate, and is assisted by the use of extra clothing and external warmth, without which cooling is excessive This hazard is more likely at the extremes of life and during illness, sedation, or anoxia, when the physiological responses are impaired The severity of the resulting hypothermia depends largely on the amount of tissue insulation, which shows much individual variability (Pugh and Edholm 1955)

As cooling progresses an initial rise in blood-pressure and heart-rate is succeeded by hypotension, with a fall in plasma-volume, and bradycardia—probably due to a direct effect on the pacemaker Peripheral pulses disappear, the circulation-time increases, and at about 86°F (30°C) atrial fibrillation or other arrhythmias may begin Shivering continues until 91°–86°F (33°–30°C) is reached, when it is succeeded by intense muscle rigidity, this disappears at about 81°F (27 2°C) At 86°F (30°C) consciousness becomes clouded, and about 77°F (25°C) the blood-pressure falls abruptly and the patient dies from cardiac failure (Alexander 1946, Crismon and Elliott 1947)

Artificial hypothermia has been studied in its surgical and therapeutic use, and immersion hypothermia is a well-recognised hazard following shipwreck, it was common in airmen forced down in the sea during the late war (Wayburn 1947) In clinical medicine hypothermia is uncommon and may pass unrecognised when it complicates severe illness which modifies its features

It has been described in alcoholism (Reincke 1875) and the lowest recorded temperature with survival (18°C) was in a young alcoholic woman following exposure (Laufman 1951) Hypothermia is an uncommon but well-recognised complication of hypopituitarism (Sheehan and Summers 1952) and myxœdema when retarded metabolism facilitates its appearance (Summers 1953, Le Marquand et al 1953, Malden 1955, Marshall and McCaughey 1956) It has been reported in the newborn, in whom the homœothermic mechanism is unstable (Mann 1955, Mann and Elliott 1957), and as a complication of chronic illness, cerebral lesions, coma, and shock (Briggs 1950, Abrahams 1954, Eason and Macnaughton 1956)

Four cases are here reported (of senility, myocardial infarction, paraplegia, and diabetic coma) in which hypothermia developed, with rectal temperatures of 80–90°F (26·7°–32·2°C).

Case-reports

Case 1.—A man, aged 86, who lived alone and had become increasingly infirm, fell in his unheated room, and lay there lightly clothed until next morning, when he was admitted. The minimum night air temperature was 43·6°F (6·5°C).

He was thin, dirty, and lice-ridden. His skin was pale, with collapsed veins, and was very cold to the touch. Body hair was scanty and there was moderate testicular atrophy. He was semiconscious and groaned hoarsely when disturbed, but did not speak. He obeyed commands to move his limbs with a very slow, incomplete response. Striking muscle rigidity was present with no shivering, and abdominal and leg reflexes were absent, though those in the arms were just present. The mouth temperature did not record on a clinical thermometer reading from 95°F (35°C), there was sinus bradycardia (rate 36 a minute), a blood-pressure of 150/70 mm Hg, and a respiration-rate of 13 a minute.

He was warmed with blankets and hot-water bottles, but after six hours had not improved, the rectal temperature was found to be 82°F (27·8°C). He was then placed in a bath initially at 98°F (36·7°C), increasing to 106°F (41·1°C). In an hour his rectal temperature rose to 90°F (32·2°C) and he was transferred back to bed (fig. 1). The clinical response was dramatic, with recovery of speech and spontaneous movement, though he remained mildly confused for some hours. The muscle rigidity disappeared, but no shivering was seen. Antibiotics and a single injection of cortisone (100 mg intramuscularly) were given after warming, and hypotension (see fig. 1) was treated with repeated intramuscular doses of mephentermine ('Mephine') 30 mg with satisfactory but temporary relief. The blood-pressure eventually stabilised at 120/80 mm Hg by the third day. Retention of urine required repeated catheterisation. Electrocardiograms showed ischæmic changes only, a leucocytosis accompanied recovery, and the 17-ketosteroid excretion was 1·6 mg per twenty-four hours; other investigations were not notable. In the fifth week he was well enough for suprapubic prostatectomy and later walked. In the ninth week he had a pulmonary embolus and then deteriorated, dying twelve weeks after admission from pulmonary infection.

At necropsy no other lesion was found. The hypothalamus and all endocrine glands appeared normal. Coronary atherosclerosis was seen without myocardial infarction.

In old age the temperature is often low, and Howell (1944) reported a mean oral reading of 97·2°F (36·2°C) over the age of 80. He noted that readings of 95°F or below were very unusual in health but not uncommon in illness. These features were well shown in this patient, whose temperature on recovery was 98°F. In the first and last weeks it was often 95°–96°F; it fell to this level after prostatectomy and to 94°F after pulmonary embolism. In this case it seemed that senility had blunted the mental and physiological responses to cold, and that cooling was favoured by emaciation.

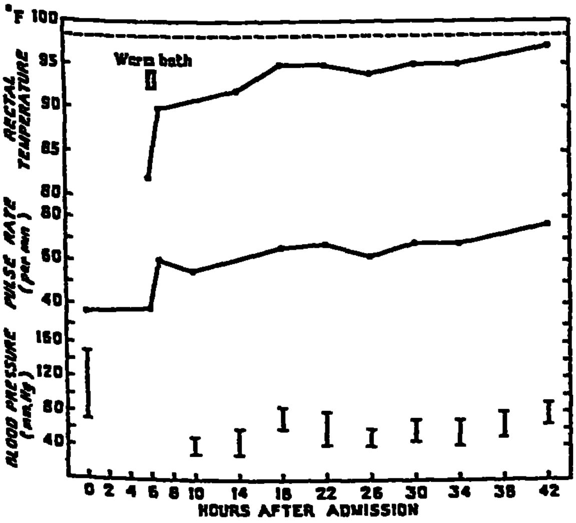

Fig. 1—Progress in case 1.

Case 2.—A man, aged 71, previously in good health, lost consciousness suddenly on the morning of Feb. 15, 1955, a particularly cold day (air temperature at 9 A.M. 34·0°F [1·1°C]) and lay lightly dressed in an unheated room until he was discovered nine hours later.

On examination he was thin, stuporose, and pale. The skin was very cold, with collapsed veins, and generalised muscle stiffness was found without shivering. Arm reflexes were reduced and leg reflexes were absent.

The initial oral temperature was recorded by a clinical thermometer as 95°F (35°C), and he had a sinus bradycardia (rate 36 a minute), a blood-pressure of 130/70 mm Hg, and a respiration-rate of 22 a minute. There were no other abnormal signs. Heavy glycosuria, mild acetonuria, and albuminuria were found, and the blood-sugar was 158 mg per 100 ml. Electrocardiograms showed ischæmic changes only.

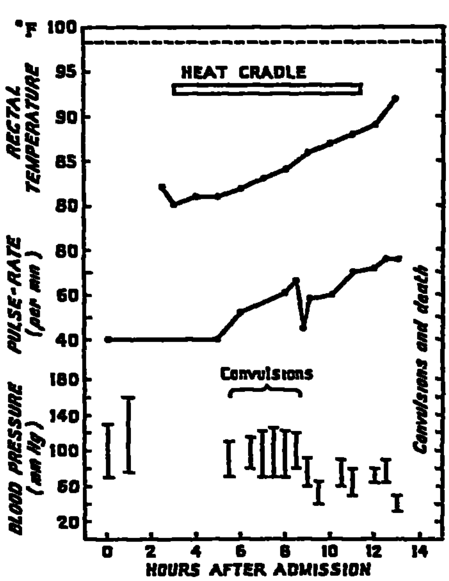

Fig. 2—Progress in case 2.

Three hours after admission there was no improvement, his rectal temperature was 80°F (26·7°C), and warming with a heat cradle was started (fig. 2). His temperature rose slowly and progressively over the next eight hours, the rise averaging 1°F an hour. During this period he had two convulsions, and after the second he lapsed into coma, the cradle was removed. Despite this his temperature continued to rise, but his condition deteriorated with deepening coma and increasing hypotension until his death fourteen hours after admission, following a third convulsion.

Necropsy showed advanced coronary atherosclerosis with almost complete obstruction of the left coronary artery $1^1/_2$ in. from its origin, and total obstruction of the right coronary artery by recent ante-mortem thrombus leading to infarction. The pituitary gland was normal histologically, but the hypothalamus was not examined.

In this patient the sudden loss of consciousness is attributed to cardiac syncope following acute coronary occlusion, with hypothermia from exposure.

Case 3 —A woman, aged 43, was admitted, after a car accident, with a fracture-dislocation of the cervical spine at c5–6, causing acute paraplegia which proved permanent

She was nursed in the open ward and burns on the buttocks, sustained in the accident, were treated by exposure Five days after admission her temperature could not be recorded with the ordinary clinical thermometer, and she complained of mild subjective coldness, with no shivering or disturbance of consciousness Her rectal temperature was then 84°F (28 9°C) At this time the air temperature was 13°F below the average for the month (day maximum air temperature 57°F [13 9°C]) Because of her sensory loss local heating was not thought suitable, she was therefore transferred to a heated sideroom where her temperature gradually rose to normal levels (fig 3) No further episodes occurred when she later returned to the ward

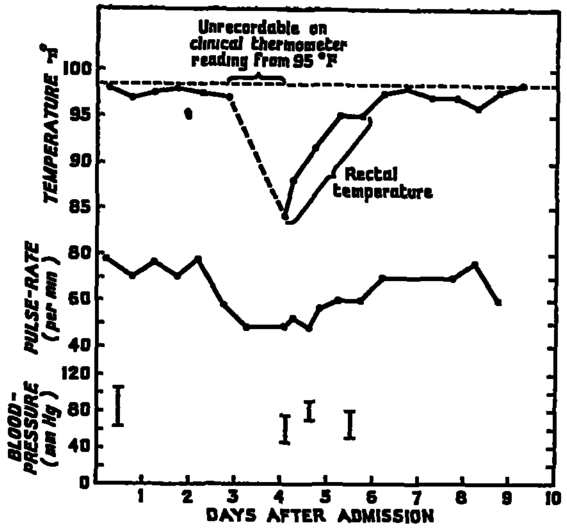

Fig 3—Progress in case 3

In this case homœothermic control below the lesion was lost, and the heat-loss incurred by the exposure treatment of burns was enough to cause hypothermia even in the summer

Case 4 —A woman, aged 44, was admitted in diabetic coma on a day when the 9 A M air temperature was 59°F (15°C) She was deeply unconscious and dehydrated, with acidotic breathing Her skin was cold and pale, and the superficial veins were much collapsed Slight shivering was seen, but there was no muscle rigidity The pulse-rate was 80 a minute, blood-pressure 60/30 mm Hg, and respiration-rate 22 a minute The rectal temperature was 90°F (32 2°C) Heavy glycosuria and acetonuria was found with a blood-sugar of 1350 mg per 100 ml and an alkali reserve of 7 mEq a litre She was resuscitated with intravenous fluids, glucose, and insulin, and noradrenaline for her hypotension It was decided to treat the hypothermia by slow warming, and she was covered by a single blanket and allowed to rewarm spontaneously in a room temperature of 70°F (21°C) Eight hours after admission her temperature had risen to 98°F (36 7°C) at a rate of 1°F per hour

In this case the hypothermia resulted from heat-loss during coma and contributed little to the clinical picture, though increasing doses of noradrenaline were needed to control the hypotension as her temperature rose

Discussion

These cases show the variety of conditions in which hypothermia may develop, and it is perhaps surprising that it is not commoner in the winter months

There may easily be delay in diagnosis because of reliance on the standard clinical thermometer, this was so in the first three cases Thus in case 2 the temperature was recorded mistakenly as 95°F (35°C) and in the others the temperatures were charted as unrecordable There were delays of six and three hours respectively in cases 1 and 2 before the depth of hypothermia was appreciated, and in case 3 the bradycardia on the previous day suggests that hypothermia was present then This difficulty was noted by Sheehan and Summers (1952), and is readily avoided by the use of a low-reading rectal thermometer whenever the ordinary clinical instrument fails to register The absence of shivering may contribute to this delay None of the present patients shivered except case 4, and she only slightly Shivering is an unreliable sign in accidental hypothermia because it is abolished by many drugs and by anoxia and does not occur in severe cases

In the first two cases the clinical features were striking, with pallor and muscle rigidity resembling rigor mortis Both had bradycardia, collapsed veins, and a normal blood-pressure, these are remarkable features in the presence of a large myocardial infarct (case 2) In contrast, case 3 had a combination of bradycardia and hypotension, the latter due to vasomotor paralysis

Consciousness was undisturbed in case 3 at 84°F (28 9°C), whereas case 1 at 82°F (27 8°C) was semiconscious and case 3 at 80°F (26 7°C) was stuporose, though cerebral anoxia probably contributed to this

Hyperglycæmia and glycosuria are reported in hypothermia and may have caused the findings in case 2

Arrhythmias developed in none of the patients, and electrocardiograms did not show the specific "injury potential" of hypothermia (Osborn 1953)

The treatment of accidental hypothermia varies with its duration and may be either rapid or slow rewarming Moderate warming should not be used, since this may release vasospasm without sufficient warming of blood Chilled blood returns to the heart, lowering the central temperature still further, and in critical cases death may result from cardiac arrest soon after starting treatment (Burton and Edholm 1955)

In acute hypothermia of rapid onset and less than twelve hours' duration, such as immersion hypothermia, rapid warming is recommended Burton and Edholm suggest a warm bath at 113°F (45°C), or an electric blanket may be used

In chronic hypothermia of slower onset and more than twelve hours' duration, the type most commonly met in clinical practice, rapid warming may lead to hypotension, as in case 1 To avoid this danger Tallbott and Burton (1952) used slow warming to resuscitate a group of patients in whom hypothermia had been induced for the treatment of advanced neoplasms Some of these patients had been maintained at 77°–80 6°F (25°–27°C) for as long as forty-eight hours They were allowed to rewarm gradually by their own metabolic efforts at about 1°F per hour in room temperatures of 70–75°F This method was used with good results in case 4, but in case 3 recovery was much slower in a room temperature of 65°F and took two days to complete This impaired response was presumably due to the defective heat conservation

Heat cradles are of doubtful use In case 2 the rise in temperature was no greater than in spontaneous rewarming, and continued more rapidly when the cradle was removed On the other hand in some instances they give excessive heat, leading to increasing shock (Gavey

1941, Grant and McMichael 1942) Their effect varies considerably, and they should be avoided since moderate warming with its attendant dangers could result

Case 2 presented a difficult problem as he deteriorated despite a slow rate of warming Murray and Bruce (1955) have used hypothermia in the treatment of severe shock due to postpartum hæmorrhage, and thought improvement was due to reduction in tachycardia and tissue oxygen requirements Their patient also had convulsions during warming Thus in case 2 accidental hypothermia itself might have protected against shock and could perhaps have been continued in the hope that the myocardium would recover enough to meet the increased demands of euthermia Deterioration on slow rewarming may therefore be an indication to continue cooling as a temporary therapeutic measure

In hypothermia there is evidence of adrenal damage and depletion of hepatic and cardiac glycogen, which may lead to heart-failure even at relatively high temperatures (Grosse-Brockhoff 1950) Cortisone, intravenous glucose, and digitalis may therefore be given during recovery

Summary

Four cases of accidental hypothermia are reported The primary conditions were senility, myocardial infarction, acute paraplegia, and diabetic coma

The diagnosis may be overlooked if a low-reading rectal thermometer is not used whenever the ordinary clinical thermometer fails to register

In treatment moderate warming should not be used, owing to the risk of increasing hypothermia and death from cardiac arrest In acute hypothermia rapid warming is indicated, but in chronic hypothermia this may cause hypotension, and spontaneous, slow warming by the patient's metabolic processes is best In circumstances where metabolism is depressed or heat conservation defective this may be insufficient, and some external warming is required

In one case accidental hypothermia may have protected against shock Deterioration during slow warming may be an indication to continue hypothermia

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MITRAL VALVOTOMY AND PREGNANCY

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DESPITE advancing knowledge and improvements in medical care pregnancy in patients with severe mitral stenosis remains hazardous, mainly because of pulmonary œdema (Jones 1951)

The surgical relief of the stenosis offers a new approach, both in rendering patients fit to undergo a pregnancy hitherto possibly deemed inadvisable and in the relief of symptoms during pregnancy It is, however, generally accepted that valvotomy rarely produces a valve of normal size, and objective evidence of improvement may be absent despite a good functional result Since the burden of pregnancy is considerable, there may be danger even after a functionally good valvotomy

The place of valvotomy during pregnancy has also been the subject of controversy

Burwell (1954) stated that it should be reserved for cases in which medical management has failed and termination is inadvisable

Glover et al (1955) considered that pregnancy increased the operative risk but that, in severe cases, valvotomy should be preferred to termination

Mulcahy (1954) felt that pregnancy was, in fact, an added indication for surgery

This paper is based upon a study of 27 women with mitral stenosis, of whom 12 were operated on during pregnancy and 15 underwent pregnancy after a successful valvotomy From our experience and from the published details of 89 other patients submitted to valvotomy during pregnancy we find that pregnancy does not appear to increase the operative risk, and operation is rarely followed by abortion We also find that difficulties may be encountered in pregnancies following apparently successful valvotomy

Material and Methods

The material consisted of 27 patients who had mitral stenosis and were attending either the department of cardiology at the Royal Infirmary or the thoracic centre at Park Hospital, Manchester All were examined in the usual manner clinically, radiologically, and electrocardiographically and allotted American Heart Association functional gradings Active infection was excluded as far as possible by clinical examination, a routine blood-count, and estimation of the erythrocyte-sedimentation rate (Wintrobe) Only 2 women were submitted to cardiac catheterisation, this was done in the usual way Pressures were recorded with a capacitance manometer and referred to a point 5 cm below the sternal notch Blood gases were analysed by the Van Slyke-Neill manometric method, and expired air in the Haldane apparatus

15 women operated on between 1952 and 1955 while not pregnant became pregnant some time after the operation All attended regularly throughout the pregnancy at the department of cardiology at the Royal Infirmary and were confined at St Mary's Hospital, Manchester Postpartum cardiological supervision has continued to the

present time The remaining 12 women were operated on between the tenth and thirty-first weeks of pregnancy They were followed up for at least six months after delivery 26 of the women were operated on either at the Royal Infirmary by Mr W F Nicholson or at Park Hospital by Mr Gordon Jack or by Mr John Dark, the remaining woman was operated on at Crumpsall Hospital by Mr Herbert Haxton

Valvotomy during Pregnancy (12 Cases)

Previous Pregnancies

5 of these patients had been previously pregnant, and 3 of these had passed through a single trouble-free pregnancy with eventual delivery of a living child The intervals since these pregnancies were long, ten years (case 6), five years (case 2), and four years (case 10) In case 11 there had been two previous pregnancies one and two years previously, both pregnancies were complicated by severe incapacity with attacks of nocturnal dyspnœa, but both went to term In case 4 three pregnancies had occurred eight, six, and four years previously, there were no cardiac symptoms before, during, or after the first pregnancy, but severe dyspnœa developed in both subsequent pregnancies, being worse in the third Nevertheless all three pregnancies went to term

Capacity for Effort before Current Pregnancy

1 patient was placed in group I (A H A classification) 8 were placed in group II, and 3 in group III By comparison with patients submitted to valvotomy apart from pregnancy these patients were less severely incapacitated before the pregnancy, but their incapacity increased during the pregnancy The sizes of the mitral openings found at operation corresponded to this clinical difference, 7 of the 12 pregnant patients having mitral orifices estimated at 1 cm or more in diameter, whereas this was so in only 7 of 15 non-pregnant patients

Indications for Valvotomy

Mitral stenosis was the sole lesion in all the cases In 8 the operation was undertaken because of attacks of nocturnal dyspnœa associated with clinical and radiological evidence of severe pulmonary congestion, and severe dyspnœa on effort The 4 other patients had severe effort dyspnœa and pulmonary congestion but no nocturnal dyspnœa 3 patients developed hæmoptysis for the first time during the pregnancy

Results of Valvotomy

The operation was undertaken at various stages of pregnancy from the tenth to the thirty-first week In 10 cases the final diameter of the valve was estimated as exceeding 3 cm , in case 11 the split was regarded as poor and the diameter estimated as more than 2 cm This patient remained dyspnœic on effort and orthopnœic and developed acute pulmonary œdema three days post partum There were several postoperative complications in some of the 11 cases with satisfactory splits

In case 4 a right hemiplegia developed six hours after the operation, but the cardiac symptoms were completely relieved, and the delivery was normal

In case 12 fever, arthralgia, and a raised erythrocyte-sedimentation rate marked the onset of acute rheumatism eight days after the operation This was associated with the onset of auricular flutter and congestive heart-failure, which proved resistant to treatment, and abortion occurred thirty days after the operation, thereafter rapid improvement took place, with the restoration of sinus rhythm and the disappearance of heart-failure and signs of rheumatic activity A year later the patient was entirely symptom-free (group I)

TABLE I—DATA OF TWELVE PATIENTS OPERATED ON WHILE PREGNANT

Case no	Age (yr)	Functional group before pregnancy	Parity	Valve size (cm)		Mode of delivery	Functional group 6 mos post partum	Remarks
				Before	After			
1	35	II	1	<1	3–4	N F T	I	
2	27	II	2	1 3	2 5	N F T	I	
3	22	III	1	<1	3	N F T	I	
4	29	II	4	1	>3	N F T	I	Right hemiplegia
5	31	III	1	<1	3	Abortion	—	Died 7 weeks after operation
6	28	II	2	0 5	4	N F T	I	
7	22	III	1	0 75	3–4	N F T	I	
8	20	II	1	1	3	N F T	I	
9	27	I	1	2	3 5	N F T	I	
10	23	II	2	1	4–5	N F T	I	
11	23	II	3	<2	>2	N F T	II	Pulm œdema 3 days post partum
12	25	II	1	1	3 5	Abortion	I	Reactivated rheumatism

N F T , normal full term

In case 5 operation was difficult, and this valve was eventually divided with a Bailey knife to give a diameter of about 3 cm Two days after the operation a cerebral embolism occurred and heart-failure developed Thirty-four days after the operation the patient was delivered of a stillborn fœtus, but heart-failure continued until death seven weeks after the operation

Final assessment six months post partum showed that 10 of the 11 survivors were symptom-free (group I), the remaining patient was classified in group III

These observations are summarised in table I

Published Cases

77 cases reported in the Anglo-American literature are summarised in table II There was only one maternal death, and there were three operatively induced abortions Most workers consider the operative results to be good, and, with one exception, all the patients appear to have gone to term and been delivered normally Including our 12 cases the total is 89 women operated on during pregnancy, with two deaths (2 2%), five abortions (5 6%), and eighty-four living children

Pregnancy following Valvotomy (15 Cases, 16 Pregnancies)

Results of Pregnancy

There were no maternal deaths, but four children were lost in sixteen pregnancies 10 of these patients had been pregnant before valvotomy, and their fifteen pregnancies had produced seven living children Six of the eight losses were due to the cardiac condition Of the four children

TABLE II—COLLECTED RESULTS OF MITRAL VALVOTOMY DURING PREGNANCY

Reference	No of cases	Maternal deaths	Abortions	Remarks
Cooley and Chapman (1952)	1	0	0	
Parkinson (1953)	1	0	0	
Burwell and Ramsey (1953)	7	1	0	
Cooley and DeBaky (1954)	5	0	0	
Crawshaw et al (1954)	12	0	0	
Mulcahy (1954)	3	0	0	
Watt et al (1954)	7	0	0	4 still pregnant at time of writing
Sellors et al (1955)	2	0	0	
Glover et al (1955)	5	0	1	
Mendelson (1955)	10	0	0	
O Connell and Mulcahy (1955)	1	0	0	Full term op
Turner and Fraser (1956)	5	0	0	
Marshall and Pantridge (1957)	18	0	2	
Present series	12	1	2	
Total	89	2 (2 2%)	2 (5 6%)	

lost in the post-valvotomy pregnancies one was eight weeks premature and survived only twenty-four hours, one was stillborn owing to strangulation by the cord, one was lost after cæsarean section at thirty-eight weeks because of toxæmia, and in the remaining case therapeutic abortion was undertaken at fourteen weeks owing to the cardiac condition Therefore only one child was lost owing to the cardiac condition Thus, from the point of view of survival of mother and child, the post-valvotomy pregnancies gave good results

Symptoms during Pregnancy

Despite these good overall results the pregnancies were by no means trouble-free

3 patients (cases 16, 24, and 28) experienced orthopnœa and attacks of nocturnal dyspnœa beginning in the second trimester

Case 23 had a severe hæmoptysis in the thirty-sixth week

Cases 13 and 14 had attacks of frank pulmonary œdema in the eighteenth week (case 13) and three days post partum (case 14)

Case 27 went into congestive heart-failure in her fifteenth week and needed supportive treatment until term

In 2 of these patients (cases 14 and 23) the operation had been regarded as satisfactory in every way The 5 others were unsatisfactory either because of adverse features present before operation (auricular fibrillation and a considerably enlarged heart in cases 18 and 27 respectively) or because the final size of the valve was considered inadequate (cases 13, 16, and 24)

Time between Operation and Pregnancy

The time elapsing between the operation and the completion of the pregnancy varied from eleven months (case 22) to nearly four years (case 18)

There appear to be no grave disadvantages associated with becoming pregnant shortly after successful valvotomy, the 2 patients (cases 19 and 22) achieving it within three months both having an uneventful pregnancy and confinement

Nor is a long interval between valvotomy and gestation necessarily disadvantageous, because case 22 underwent a second pregnancy uneventfully two years after the first If the interval is long, a careful reassessment must be made to discover if there has been deterioration, this is exemplified by case 28 This patient, who appears in table I as case 3 because she was operated on during pregnancy, is of especial interest, and her case is therefore reported in full

Case 3 (28)—A woman, aged 22, was seen in September, 1953, when she was eight weeks pregnant She had been short of breath on exertion for two years, and six months previously had had an attack of acute dyspnœa characterised by the production of frothy pink sputum Examination revealed pure "tight" mitral stenosis with radiological evidence of moderate pulmonary congestion and the electrocardiographic appearances of right ventricular hypertrophy

Operation and Progress—Mitral valvotomy was done on Oct 7, 1953 The valve was estimated initially to be 0·7 cm in diameter and was enlarged to more than 3·0 cm Convalescence was uneventful Biopsy of the auricular appendage showed "active rheumatism" The patient kept well during the remainder of the pregnancy and had a normal labour on May 14, 1954 When finally assessed in August, 1954, she admitted to no symptoms and was classified as group I, although neither radiography nor electrocardiography showed any appreciable improvement since before the operation During the winter of 1955–56 she again noticed shortness of breath on effort but improved with the warmer weather

Next pregnancy—In January, 1957, she attended again when sixteen weeks pregnant, she had become much more short of breath and had had three nocturnal attacks of dyspnœa with frothy white sputum On examination, in addition to the signs in the heart, there were crepitations at both lung bases At cardiac catheterisation on March 1, 1957, the mean resting pulmonary arterial pressure was 61 mm Hg, the pulmonary capillary venous pressure 31 mm Hg, and the cardiac output 5·7 litres a minute Medical management was adopted, the patient at present requires a good deal of rest and a restricted intake of salt

It is difficult to know whether the valve has become stenosed again Although the split was good both in the surgeon's estimate and, initially, in terms of function, objective evidence of improvement was lacking Clearly, however, an apparently successful valvotomy followed by trouble-free pregnancy and confinement does not guarantee that subsequent pregnancies will be equally trouble-free Had this patient not previously been operated on, the symptoms, the physical findings, and the results of catheterisation were such that operation would probably have been advised

These data are summarised in tables III and IV

Discussion

Despite the fears expressed by Burwell (1954) it seems that the complication of pregnancy does not add appreciably to the operative risk, the operative mortality of 2·2% approximates closely to the anticipated mortality in a group of patients in functional groups II and III It

TABLE III—DATA OF PATIENTS BECOMING PREGNANT AFTER VALVOTOMY

Case no	Age (yr)	Cardiac rhythm	Time after operation (mos)	Functional group		Valve size (cm.)		Complications during pregnancy	Mode of delivery
				Before	After	Before	After		
13	19	Sinus	24	III	II	Tight	N A	Pulm œdema in 18th wk.	N F T D
14	22	Sinus	27	II	I	1	3	Pulm œdema, 3 days post partum	N F T D
15	25	Auricular fibrillation	19	II	I	0·7	3	Nil	8 wk. premature (child died)
16	28	Sinus	16	III	II	N A	N A	Nocturnal dyspnœa and hæmoptysis	Full time stillbirth (knotted cord)
17	35	Sinus	21	III	I	<1	3	Nil	N F T D
18	30	Auricular fibrillation	45	IV	II	0·5	2–3	—	Terminated in 14th wk, deteriorating
19	26	Sinus	12	III	I	<1	3	Nil	N F T D
20	29	Sinus	29	III	I	0·5	2·5–3	Nil	N F T D
21	20	Sinus	14	II	I	<1·5	2·5–3	Nil	N F T D
22	30	Sinus	11	III	I	1	4	Nil	N F T D
			35					Nil	N F T D
23	28	Sinus	29	II	I	1	3–4	Hæmoptysis in 36th wk	Cæsarean section in 38th wk (toxæmia) child died
24	32	Sinus	29	II	II	1·5	2·5	Nocturnal dyspnœa in 30th wk	N F T D
25	25	Sinus	29	III	II	0·5	2·5	Nil	N F T D
26	35	Sinus	23	III	I	1	3	Nil	N F T D
27	31	Auricular fibrillation	22	III	II	1	3	Congestive heart failure from 15th to 40th wk	N F T D
*28	27	Sinus	36	III	I	0·7	3	Nocturnal dyspnœa 12th wk	Still pregnant

* Case 3 in table I N A not available. N F T D normal full term delivery

TABLE IV—COURSE AND RESULT OF PREGNANCY BEFORE AND AFTER VALVOTOMY IN TEN CASES

Case no	Previous pregnancies		Date of operation	Subsequent pregnancies	
	Date	Mode of delivery and complications		Mode of delivery	Complications
15	1952 1954	Spontaneous abortion at 3 mos Spontaneous abortion at 3 mos	March 8, 1954	8 wk prem	Child survived 24 hr
16	1947 1952	N F T D Therapeutic abortion	Feb 11, 1954	N F T D	Stillbirth, knotted cord
17	1942	N F T D	March 8, 1954	N F T D	Nocturnal dyspnœa and hæmoptysis
18	1945	N F T D, dyspnœa and hæmoptysis	April 24, 1952	Termin in 14th wk	Congestive heart-failure
20	1950 1952	Induced labour, dyspnœa Terminated in 14th wk dyspnœa	May 4, 1953	N F T D	
21	1952 *	N F T D, P N D at 6 mos	June 13, 1955	N F T D	Hæmoptysis in 36th wk
22	1946 1949	N F T D N F T D	June 21, 1954	1955 N F T D 1957 N F T D	
25	1950 1952	N F T D, pulm œdema 3 days post partum Terminated in 12th wk dyspnœa	April 29, 1953	N F T D	
26	1943	N F T D	Nov 4, 1954	N F T D	
27	1953	Terminated in 22nd wk. dyspnœa	May 2, 1955	N F T D	

N F T D, normal full-term delivery S B, stillborn P N D, paroxysmal nocturnal dyspnœa

is difficult to contrast these results with those obtained by *medical management, because data from comparable* series of cases are not available.

Morgan Jones (1952) found the maternal mortality due to heart-disease in 543 cases in which there was no definite cardiac contraindication to pregnancy to be 0·7%. In 343 of these cases, in which there were symptoms and some pulmonary congestion, the mortality was 1·1%. The maternal mortality is probably increased by valvotomy during pregnancy by contrast with medical management, but this increased risk is certainly not more than that which would be incurred if the pregnancy was allowed to continue without operation and valvotomy was done post partum. Correct perspective therefore demands taking into account how many patients would ultimately come to operation and whether pregnancy merely brings forward the time at which the operation is done.

It has been observed previously (Marshall and Pantridge 1957) that the added burden of pregnancy may cause a moderately stenosed valve (1·5–2·0 cm in diameter) to simulate tight stenosis in the non-pregnant state, but, irrespective of the pregnancy, operation was merited on the basis of the symptoms and signs and the size of the valve in 8 of our 12 pregnant patients. It must be admitted that, had they not become pregnant, operation would not have been advised because of the symptoms in the remaining 4, and it is difficult to say whether it would ultimately have been required.

These women with only moderate stenosis could have been managed medically, but the possibility of future pregnancies, the uncertain prognosis, and the fact that 3 of our 4 such patients were functionally improved when their postpartum state was compared with their condition before pregnancy all argue in favour of operation.

Surgery does not appear dangerous to the fœtus. The fœtal mortality of 5·6% (table II) compares favourably with that of 8·6% cited by Hamilton (1947) and 10·2% in 990 pregnancies complicating all forms of heart-disease seen in this department in 1946–51, more than half of them (6·4%) being terminated because of the heart-disease (unpublished data). The anticipated abortion-rate in healthy women from the twelfth week of pregnancy onwards is about 2% (Eastman 1955).

We therefore feel that, if during pregnancy the symptoms are severe enough to warrant it and the valve is technically suitable, valvotomy is the treatment of choice. Even in cases seen within the first few weeks of pregnancy we doubt if Burwell and Metcalf (1954) are correct in regarding termination as the safest course. In favour of termination the fact that, if valvotomy is attempted and fails, the pregnancy may by then have progressed so far that there is no longer any alternative to going on to term. This is a valid criticism, but it must be remembered that termination is not entirely safe, and 2 of the deaths due to heart-disease in Morgan Jones' (1951) series of 352 cases followed termination. Our experience does not suggest a preferential time for surgery. It seems reasonable to operate sufficiently early for convalescence to remain uncomplicated by premature labour, but the patient of O'Connell and Mulcahy (1955) was operated on at term with good results.

Our findings emphasise that patients who have had a good operation both in terms of increased size of the valve and subsequent functional improvement may nevertheless encounter difficulties during pregnancy. 10 of our patients were considered excellent results in every way, yet 1 had pulmonary œdema three days post partum, and 1 other had attacks of nocturnal dyspnœa as early as the twelfth week. Glover et al. (1955) also report a case in which, after an apparently successful valvotomy, pregnancy was complicated by postpartum pulmonary œdema, but Harken (1953) reported fifteen uncomplicated pregnancies and confinements following operation.

These paradoxical observations again reflect the fact that, whereas pregnancy may cause moderate stenosis to simulate tight stenosis, the operative conversion of tight to moderate stenosis may be sufficient to give a good functional result in a non-pregnant woman.

The work of Donald et al. (1957) suggests that a considerable degree of narrowing of the valve may persist after operation, because in 8 of 9 patients classified as excellent results, the resting pulmonary capillary venous pressure was 20 mm Hg or higher. Since the cardiac output was subnormal in most of these patients, it can be appreciated that the increased cardiac output of pregnancy may cause a considerable increase in pulmonary capillary venous pressure. In 2 of their "excellent" cases Donald et al. found that raising the output by 75% by exercise increased the pulmonary capillary venous pressure from 23 to 57 mm Hg and from 28 to 49 mm Hg. In 5 of our 6 cases in which the operative results were less than excellent severe symptoms were encountered during pregnancy. It therefore appears that, although a woman who has undergone a successful operation and subsequently is placed in group I will usually go through pregnancy without trouble, this is not necessarily the case, and difficulties are to be expected in those with less successful operative results.

In women operated on before conception the intervals *between operation and confinement varied from eleven* to forty-five months, and there is no evidence that any particular interval is to be preferred It seems reasonable to delay conception until an accurate postoperative assessment can be made, and this probably cannot be made in less than six months After this there are strong arguments for encouraging early conception, because probably in a proportion of patients a good result may not be lasting (Baker et al 1955) There is therefore a greater need for careful assessment if the interval after operation is long This tendency to deterioration may partly explain the relative absence of trouble in patients operated on during pregnancy by contrast with those in whom the operation antedated pregancy, but (as already noted) the two groups are not comparable as regards the severity of the disease

Summary and Conclusions

The results in 12 patients with mitral stenosis submitted to mitral valvotomy while pregnant are reported, together with those in 77 published cases

In these 89 cases the operative mortality was 2 2% and the abortion-rate 5 6%

It is concluded that (1) pregnancy does not appear to increase the operative risk, (2) by contrast with medical management the operation does not increase the fœtal mortality, and (3) in suitable cases valvotomy seems preferable to termination

Seventeen pregnancies in 16 patients who had previously undergone mitral valvotomy are reported twelve living children were obtained by normal full-term delivery, one pregnancy was terminated at fourteen weeks because of heart-failure, 1 patient was delivered by cæsarean section at thirty-eight weeks because of toxæmia, there were two fœtal deaths unrelated to the mothers' heart condition, and 1 patient is still pregnant

Symptoms due to severe pulmonary congestion were encountered in 3 of 10 patients placed in function group I after the operation and in 5 of 6 patients placed in group II

It is concluded that (1) although pregnancy following successful valvotomy is usually safe, difficulties may be encountered, (2) a technically unsatisfactory operation, even if followed by reasonable functional improvement, is unlikely to permit of a trouble-free pregnancy, and (3) assessment of fitness for pregnancy cannot be satisfactorily undertaken sooner than six months after the operation Delay in conception after this may be disadvantageous

We thank Mr John Dark, Mr Herbert Haxton, and Mr Gordon Jack for their cooperation and help

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POTASSIUM DEFICIENCY IN LIVER DISEASE
CAUSING MUSCULAR WEAKNESS AND POLYURIA

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Low serum-potassium levels in patients with liver disease have been reported several times in recent years, but without any clinical consequence beyond changes in the electrocardiogram

Severe potassium-deficiency in the two patients with cirrhosis of the liver described here caused muscular weakness and nephropathy The potassium deficiency was attributed to excessive loss of potassium in the urine, the cause and significance of such loss are discussed

Case-reports

FIRST CASE

A married woman, aged 30, was admitted to the Derbyshire Royal Infirmary on June 25, 1954 She was very ill on admission The history was of fatigue since the birth of her second child a year previously, jaundice for 10 weeks, weakness of her limbs for 6 weeks, which made it necessary for her to use a stick in the house and impossible for her to do her housework, and which caused her to fall frequently, thirst and frequency of micturition for six weeks, and amenorrhœa for two months

The prominent signs were extreme air-hunger, jaundice, enlargement of the liver and spleen, increased pigmentation, spider nævi, and great weakness She could not sit without support, and her voice trailed away into silence when trying to answer questions The patellar reflexes were not obtainable and the tendo-achillis reflexes were very weak

Investigation and Treatment

The alkali reserve was 10 8 mEq per litre of plasma, the serum-sodium 130 mEq, the plasma-chloride 98 mEq, the serum-potassium 1 7 mEq, the blood-urea 48 mg per 100 ml, and the serum-bilirubin 3 7 mg, the other liver-function tests were grossly deranged The urine pH was 7 1 on the day of admission, and 7 3 and 7 4 on the second and third days of treatment There were between 15 and 20 pus cells in the urine in each high-power field The electrocardiogram (E C G) showed evidence of potassium depletion (fig 1)

The alkali reserve was restored in 2 days by intensive oral sodium-bicarbonate therapy, but it was 24 days before the serum-potassium reached 3 4 mEq per litre with a daily dose of 16 g of potassium chloride (214 mEq) for the first week, by this time all reflexes had returned, and doses of 8 g daily

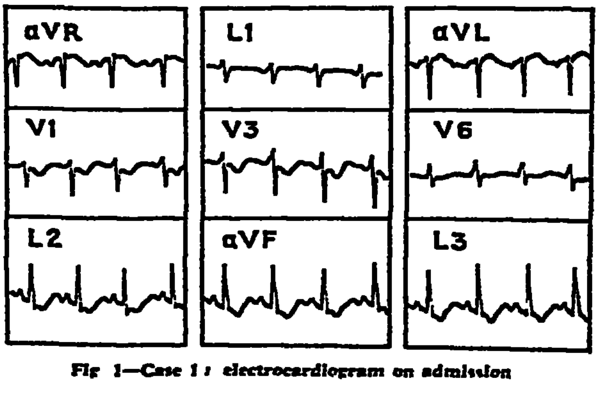

Fig 1—Case 1: electrocardiogram on admission

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(107 mEq) were given thereafter The electrocardiographic changes improved slowly and were closely correlated with the rising serum-potassium level, becoming normal after 25 days' treatment The blood-urea fell to normal levels (23–30 mg per 100 ml) after 10 days of therapy Jaundice disappeared, the serum-bilirubin fell to normal levels but the other liver-function tests remained grossly deranged There was no tetany and the lowest level of serum-calcium was 8 6 mg per 100 ml on the day of admission

The specific gravity (S G) of the urine throughout the 24 hours varied only between 1008 and 1010, it was still 1010 after 12 hours without fluid, and dropped only to 1006 after a litre of fluid The daily sodium output in the urine was 170 mEq , and the potassium output was 46 mEq on the 6th day, 39 mEq on the 7th day, and 79 mEq on the 26th day, when the oral supplements of potassium chloride were 214 mEq , 214 mEq , and 107 mEq respectively On the 4th and 5th days the CO_2 content of the urine was 8 7 mEq and 6 5 mEq per litre when the oral dose of sodium bicarbonate was 12 g (143 mEq) daily Chromatography of the urine (Prof C E Dent) showed no excess of aminoacids

Subsequent Course

She was discharged after 4 weeks, taking as maintenance therapy potassium chloride 8 g and sodium bicarbonate 16 g daily She remained well and was readmitted 6 weeks later for investigation The liver-function tests were still abnormal, but the pus cells had disappeared from the urine and the ability to concentrate the urine was restored, the S G after a 12-hour fluid-fast was 1020 and the S G on dilution 1006 Alkalinisation by acetazolamide (250 mg) increased the urine pH from 7 1 to 7 8, and acidification by ammonium chloride (5 g) decreased the pH from 7 1 to 6 3 The daily urinary output averaged just over 4 litres

She remained well on the same maintenance therapy, and was readmitted for investigation 15 months later Treatment by sodium bicarbonate and potassium chloride was stopped for 2 weeks In this time the alkali reserve fell from 24 mEq to 14 mEq per litre, the serum-potassium from 4 0 mEq to 3 4 mEq per litre, and the urinary potassium from 96 mEq to 28 mEq in 24 hours Treatment was recommenced before an operation for the removal of a rectal polyp which was causing some rectal hæmorrhage Bleeding was severe after the operation and hepatic failure supervened She was restored by treatment and discharged herself 2 weeks later

5 days later she was readmitted in hepatic failure and died At necropsy there was multilobular cirrhosis of the liver There was no tumour in the adrenal cortex Mild chronic pyelonephritis was present, with focal tubular calcification A specimen of urine was sent to Dr A H Gowenlock, 10 days before death, he reported that it contained 20 5 µg of aldosterone in 24 hours (normal 4 6 to 23 5 µg) She was excreting 119 mEq of potassium daily at the time of the estimation, and was taking 8 g daily of potassium chloride (107 mEq)

SECOND CASE

A man, aged 49, was first admitted to St Bartholomew's Hospital in May, 1954 He had been in another hospital in November, 1953, for a hæmatemesis, which was followed by temporary ascites and œdema Hæmatemesis recurred in February, 1954, and was followed by ascites A month before admission he had no ascites, but the liver and spleen had become palpable and liver-function tests were abnormal for the first time He had been jaundiced at the age of 7 He habitually drank stout

The liver and spleen were enlarged, there were three spider nævi, palmar erythema, and small hæmorrhoids, the blood-pressure was 130/70 mm Hg, and weight 155 lb The urine was normal (daily volume 1 5 litres) There was moderate anæmia and thrombocytopenia (platelets 115,000 per c mm) The serum-proteins were 7 8 g (albumin 4 8, globulin 3 0) and bilirubin 0 5 mg per 100 ml , pseudocholinesterase 51 units (normal 55 to 125 units), prothrombin level 33% of normal radiograph of the chest was normal, swallowed barium howed small varices at the lower end of the œsophagus, on excretion urography anatomy and function were normal

At operation (Mr A H Hunt) the liver appeared cirrhotic After biopsy, the portal vein was anastomosed to the inferior vena cava Recovery was uneventful The liver biopsy showed portal cirrhosis

During the next 6 months the spleen became impalpable For a further year he remained well, though thrombocytopenia persisted (platelets about 70,000 per c mm), his liver enlarged, and his weight gradually increased In March, 1956, he was weak and breathless on exertion, with hepatic fœtor and ankle œdema

Second Admission

He was readmitted on May 10, 1956 Polyuria and thirst had been noticed for several weeks He was euphoric and confused, with a fine tremor of the fingers There was œdema to the waist and moderate ascites, weight 178 lb Secondary sexual hair was sparse, the skin was brown, and there was slight jaundice The pulse was collapsing, and the blood-pressure 180/45 mm Hg, a harsh systolic murmur was loudest at the apex, there were moist sounds at the left lung base The firm, rounded liver-edge was 3 cm below the costal margin He drank 4 to 6 litres of fluid daily and passed much dilute urine (S G 1004–1005) Chest radiography showed pulmonary vascular engorgement, enlargement of the heart, and small bilateral pleural effusions The E C G showed widespread abnormalities of the ST segments and T waves There was a mild anæmia, the platelet count had risen to normal Serum-

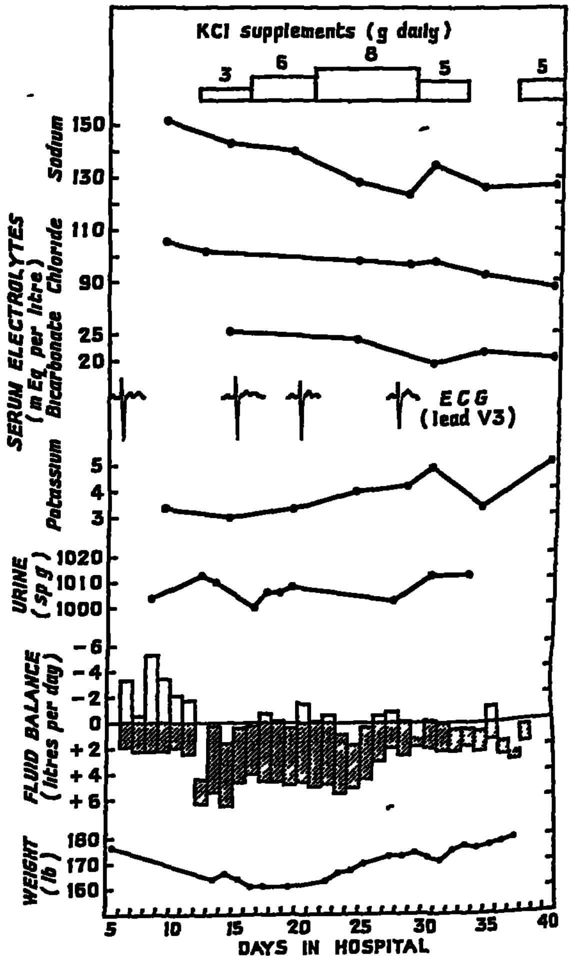

Fig 2—Case 2 potassium supplements, serum electrolytes, E C.G , S G of urine, fluid-balance, and body-weight during last admission Fluid intake is plotted downwards from the zero line, and urine output upwards Collection incomplete on days *29 and 37*

proteins were 5 8 g per 100 ml (albumin 2 6, globulin 3 2) and bilirubin 5 7 mg per 100 ml , pseudocholinesterase 35 units, prothrombin level 18% of normal, alkaline phosphatase 27 5 King-Armstrong units The blood-urea was 19 mg per 100 ml

On May 14 (day 5 of fig 2) he became drowsy, and was given oral chlortetracycline and sodium glutamate (23 g daily) On a fluid intake of 2 litres daily he continued to pass large quantities of dilute urine (fig 2) His weight, œdema, jaundice, and drowsiness diminished Serum electrolytes on day 9 were sodium 152, potassium 3 3, and chloride 105 mEq per litre

Stupor developed on day 12, with flapping tremor, increased tendon-jerks and fœtor Protein was withheld and large doses of glucose were given by mouth There was heavy glycosuria and the blood sugar was 460 mg per 100 ml Instead of sodium glutamate, glutamic acid was given (20 g daily), and oral potassium chloride was started (3 g daily)

In the next 2 days he improved to his original state of mild confusion, but flapping tremor persisted Ascites was absent on day 14, and the liver smaller The blood-sugar was 128 mg per 100 ml , and glycosuria ceased Serum-electrolytes were sodium 143 mEq , potassium 2 9 mEq , bicarbonate 25 7 mEq per litre, calcium 9 6 mg per 100 ml The E C G showed further ST-segment changes and prominent U waves, as in hypokalæmia (Bellet 1955) He was allowed 20 g of protein daily, 200 g of carbohydrate, and 500 mg of salt

The daily dose of potassium chloride was increased to 6 g on day 16, and to 8 g on day 21, but the serum-potassium rose only slowly, and improvement of the E C G was no more rapid (fig 2) Polyuria and polydipsia continued Fluid deprivation was tolerated for only 6 hours on day 18, the minimum urine-flow was 3 ml a minute, and the maximum S G was 100 Next day he was given 10 units of vasopressin ('Pitressin') subcutaneously, and was allowed to drink 400 ml per hour In the first hour the urine S G reached 1008 The rate of urine-flow fell from 5 to a minimum of 3 3 ml per minute (during the 2nd hour)

During day 22, when his intake of sodium was 9 mEq , and his dietary potassium being supplemented by 107 mEq of potassium chloride, the urine contained 70 mEq of sodium, 97 mEq of potassium, and 18 9 g of urea in 5 4 litres—suggesting potassium retention accompanied by sodium loss as in the repair of a potassium deficit The daily urinary output of calcium was 342 mg An oral glucose-tolerance test on day 21 gave a high normal curve Urea clearance was normal on day 24 Radiography of the pituitary fossa showed a small area of vascular calcification superimposed on the sella in the lateral view, but no other abnormality

During the 4th week his weight increased again, with increasing œdema, but without ascites The liver ceased to be palpable Clinical signs of an overactive circulation were supported by measurement of blood-flow through the feet, which was about four times the normal (Dr R. S Duff) Fluoroscopy showed a large left ventricle and exaggerated pulsation of the pulmonary vessels The blood-pressure had fallen gradually to 115/40 mm Hg

At the end of the 4th week the E C G was less abnormal, the serum-potassium was up to 4 2 mEq , and the serum-sodium down to 124 mEq per litre Excretion urography showed only faint dye shadows, but normal anatomy The daily output of urine declined to about 2 litres, and thirst ceased The serum-potassium level rose to 4 9 mEq per litre on day 30, potassium chloride was omitted for 6 days, but given again after the serum-potassium was found to have fallen to 3 3 mEq per litre The low serum-sodium was not appreciably influenced by substitution of sodium glutamate for glutamic acid increasing the daily intake of sodium to 36 mEq on day 28 and to 108 mEq on day 37

On day 34 the serum-proteins were 4 6 g per 100 ml (albumin 1 7, globulin 2 9), and œdema was generalised The area of liver dullness disappeared Epistaxes, increasing stupor, and ankle clonus heralded the coma in which he died on the 40th day Permission for necropsy was refused

Discussion

The severe muscular weakness of the first patient was due to potassium deficiency, which also caused characteristic electrocardiographic changes Both responded gradually to potassium supplements while the serum-potassium level rose slowly to normal Her urine was of low and almost constant specific gravity, with a high pH and bicarbonate concentration which, taken with the low serum-bicarbonate concentration, was indicative of defective tubular reabsorption of water and bicarbonate There was a minor degree of nitrogen retention and of pyuria, and there was some histological evidence of pyelonephritis at necropsy The renal function improved considerably with potassium repletion Moreover, she had symptoms of potassium deficit before those of renal damage The findings can well be explained as due to the nephropathy of potassium depletion (Relman and Schwartz 1956) with a pyelonephritis superimposed (Eales and Linder 1956) Calcification has been noted in the renal tubules of potassium-deficient animals (Follis et al 1942), but Fourman and McCance (1955) implied that renal calcification in their patient was the natural result of the increased calcium excretion of acidosis

The renal loss of bicarbonate was presumably the cause of the acidosis, and this would sufficiently explain the absence of the alkalosis which is expected in potassium deficiency "Renal tubular acidosis" is characterised by potassium loss, but in this condition the administration of an adequate amount of sodium bicarbonate is usually enough to prevent loss of potassium The plasma-chloride was *never raised in case 1*

The second patient had a vasopressin-resistant diabetes insipidus which diminished as the serum-potassium and the E C G gradually returned towards normal on large potassium supplements Glycosuria on days 12 and 13 raised the S G of the urine to 1012 and 1010, as happens with an osmotic load in classical diabetes insipidus (Brodsky and Rapoport 1951), otherwise the S G did not exceed 1008 in the first 4 weeks Hyposthenuria unresponsive to vasopressin is a recognised feature of the nephropathy of potassium depletion (Relman and Schwartz 1956) It is also seen as a familial condition, and rarely in a variety of renal disorders which are unlikely to have been present in this patient There may have been some "renal tubular acidosis", since the serum-bicarbonate level was not raised, but a low serum bicarbonate level in early hepatic coma may also be due to hyperventilation (Vanamee et al 1956)

Neither patient had frank or latent tetany, its relation to potassium deficiency and acid-base balance is still obscure (Fourman and McCance 1955)

We conclude that there was severe potassium deficiency in both cases, causing paralysis and probably nephropathy in the first, and vasopressin-resistant diabetes insipidus in the second Repletion with potassium, which required continued administration of large doses, was of great benefit in the first case and probably useful in the second

Cause of the Potassium Deficiency

There was no reason to suspect deficient potassium intake in either patient, and neither had chronic diarrhœa to suggest loss from the gut So renal loss is most likely Mahler and Stanbury (1956) collected figures for the renal potassium output of normal people at various serum-potassium levels, by this standard all the output figures for our patients are excessive, except the last in case 1, which is high normal

Urinary excretion of potassium is excessive in some cases of primary renal disease Since potassium deficiency causes renal disorder, the distinction can be difficult The history of case 1 and her improvement on potassium supplements suggest that pyelonephritis was a consequence of potassium deficiency rather than its cause In case 2, the absence of other signs indicates that the renal disorder was solely due to potassium deficiency Renal loss of potassium can be caused by mercurial diuretics and by acetazolamide, but neither was given It can also be induced by heavy osmotic loads of some sodium salts (Rapoport et al 1949) Sodium glutamate may have had an effect of this kind in case 2, but it is unlikely to have been important

Aldosterone causes renal loss of potassium, especially in patients with primary aldosteronism (Conn 1955) Case 1 did not have an adrenal tumour, her urinary excretion of aldosterone was only high normal, and none of the other features of primary aldosteronism was present Case 2 had a high serum-sodium level only during restriction of fluid intake, and impaired glucose tolerance, this may be seen in primary aldosteronism (Hewlett et al 1957), but here may have been due to liver damage Neither had definite hypertension patients with cirrhosis of the liver, who have peripheral vasodilatation and a high cardiac output (Kowalski et al 1954), rarely have hypertension, and may lose it (Loyke 1955)

The interactions of steroid hormones on electrolyte balance are still as uncertain as are the effects of liver disease on steroid hormone metabolism (Cameron 1957) But aldosterone is the steroid most likely to cause electrolyte effects like those of deoxycortone acetate (D C A) Repeated large doses of D C A can cause a condition in dogs very like primary aldosteronism in man (Kuhlmann et al 1939, Ragan et al 1940) A man has developed polyuria, polydipsia, paralysis, tetany, and E C G changes, all probably due to potassium deficiency, after a large dose of D C A (Moehlig and Jaffe 1942) The patients of Luft and Sjögren (1953), given D C A for many weeks, had a steadily rising urinary output of calcium, while case 2 had a high urinary calcium output (which may have contributed to his polyuria) without a high serum-calcium level

The urinary output of aldosterone is usually high in patients with œdema or ascites from cirrhosis of the liver, and is correlated with renal retention of sodium (Wolff et al 1956) In this, as in other forms of secondary aldosteronism (Conn 1956), sodium retention is the dominant electrolyte effect But potassium loss is a known hazard of congestive heart-failure and of the nephrotic syndrome, it may be more common in cirrhosis than is usually thought Renal potassium loss due to aldosterone is likely to depend on the level of sodium intake (Relman and Schwartz 1957), and an unrecognised high salt intake could have been a factor in the development of potassium deficiency in our patients

The need for potassium in the treatment of severe acute liver disease was pointed out by Latner (1950), the treatment of hepatic coma includes supplementary potassium (Sherlock et al 1956) Low serum-potassium levels in a variety of more chronic liver disorders, especially cirrhosis, were reported by Wang (1952), and were common in patients with cirrhosis and œdema (Amatuzio et al 1952) Patients with cirrhosis, even without œdema or ascites, had a low exchangeable potassium (Aikawa et al 1953) Negative potassium balance due to renal loss has been reported in a few patients with liver disease (Fongi et al 1954) Electrocardiographic change is the only consequence attributed to potassium deficiency in these reports But in our patients the effects of potassium deficiency were so severe as to suggest that it is a complication of liver disease worth search and treatment—especially because the nephropathy of potassium depletion is reversible in its early stages (Relman and Schwartz 1956)

The paradoxical conjunction of œdema due to cirrhosis with diabetes insipidus (whether responding to vasopressin or not) has not been recorded before Classical diabetes insipidus can exist with œdema of the " secondary aldosteronism " type, as in the nephrotic syndrome (Landau and Wajsman 1934) Vasopressin-resistant diabetes insipidus with œdema has been reported by White (1954) in a patient with cerebral metastases A lesion of the tuber cinereum was thought by Biggart (1937) to be the cause of the development of resistance to vasopressin in a patient with diabetes insipidus, evidence is now accumulating that the secretion of aldosterone may be controlled by the hypothalamus (*Lancet* 1957) There was probably no lesion of the pituitary or hypothalamus in case 2

Summary

Two patients with chronic liver disease were found to have severe potassium deficiency

A woman, aged 30, presented with jaundice, muscular weakness, and polyuria She had hypokalæmia with electrocardiographic changes and renal functional defects like those of potassium deficiency, and severe acidosis The acidosis was of renal tubular origin, and was rapidly corrected by sodium bicarbonate Large potassium supplements gradually corrected the other abnormalities, but signs of liver damage persisted, and she died 2 years later of hepatic failure Necropsy showed multilobular cirrhosis and a mild chronic pyelonephritis

A man, aged 49, had a portacaval anastomosis for recurrent hæmatemesis due to portal cirrhosis His liver function gradually deteriorated during the next two years, until he was admitted with œdema and a diabetes insipidus resistant to vasopressin, he had hypokalæmia and corresponding electrocardiographic changes Potassium repletion restored his ability to concentrate the urine before he died of hepatic failure

The potassium deficiency is attributed to renal loss of potassium in both cases, and the possible causes of such loss are discussed, with particular reference to aldosterone

We are grateful to Prof C E Dent and Dr A H Gowenlock for their special investigations of the urine in case 1, to Dr G W Hayward and Mr A H Hunt for permission to report case 2, and to Dr R S Duff for measuring peripheral blood-flow

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PILONIDAL SINUS OF THE UMBILICUS

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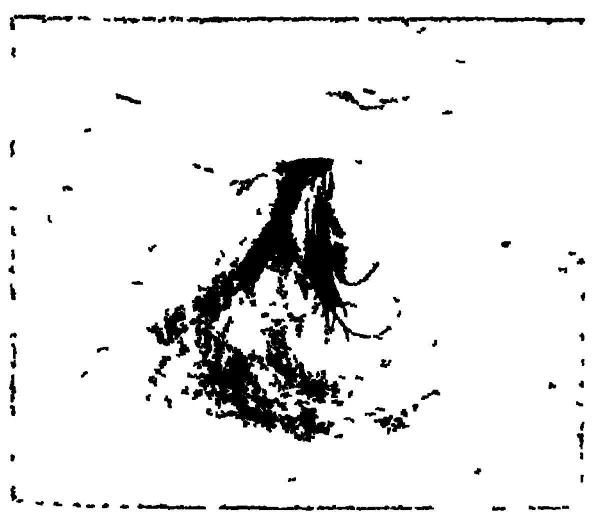
Pilonidal sinus is of perennial interest particularly because of its sites and the theories about its ætiology The case reported here provides yet another link in the important chain of evidence that pilonidal sinuses are unlikely to be congenital

Soon after the first descriptions of pilonidal sinus in the usual sacrococcygeal position by Anderson (1847) that involving the umbilicus was noted by Warren (1854) Patey and Scarff (1946) reported and discussed the first of a collection of cases of pilonidal sinus in the hands and fingers of hairdressers, and in so doing caused a complete swing in the tenets of ætiology of all pilonidal sinuses, away from the theories of developmental causes towards those observations showing acquired mechanical and secondary infective origins, the hairs being "sucked" into the skin, especially wherever there is a cleft or a web between parts of the body Thus pilonidal sinus has been seen in the interdigital webs of the toes (Brearley 1955), in the axilla (Aird 1952), and in the perineum (Smith 1948, Edwards and Riemann 1950)

Patey and Williams (1956) described a pilonidal sinus of the umbilicus They showed that there was a uniform, and not haphazard, orientation of hairs in the sinus, the roots being directed always towards the lining of the cavity This seems to be a constant feature of pilonidal sinuses (Weale 1955), and it might reasonably be supposed that such an orientation of the roots should favour the theories that hold that such sinuses are developmental abnormalities, a haphazard arrangement favouring the "acquired" theory However, Patey and Williams feel that, because the lesion of the umbilicus is most likely to be an acquired lesion, the uniform orientation shown cannot be the determining indication that the lesion is of congenital origin Patey and Scarff (1955) suggest that all loose hairs will, even if sucked in, be propelled root first into the skin by reason of the direction of overlap of their scales



The bundle of hairs, uniformly oriented coming out of the umbilicus with a secondary opening above. The skin around has been shaved.

In the present case there is a uniform orientation of hairs (see figure), which entered the skin via the umbilicus, there being a secondary opening above

Case-report

An obese dark-skinned man, aged 56, moderately hirsute, was admitted for cholecystectomy Examination of his abdomen revealed a bundle of hairs presenting at the umbilicus, coming out of a short track $^1/_4$ inch long There had been no discharge or pain. The patient had not noticed it before, there was no history of the lesion in the days of adolescence or early adult life before he became so hirsute Before his operation the hairs were removed quite easily The sinus was not excised

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EXTRAPERITONEAL COLOSTOMY

C Patrick Sames
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Lateral-space obstruction is a well-recognised complication of left iliac colostomy Closure of the lateral space can be technically quite difficult, and may not altogether preclude possibilities of strangulation of small bowel Whether the space is closed from above or from below, loops of bowel can still be caught in the sulcus which is formed Some surgeons resort to a midline colostomy, with a lateral space so large that strangulation is unlikely

The similar risk of intestinal obstruction being caused when a drainage tube is passed obliquely into the peritoneal cavity (after anterior resection or some similar procedure in the pelvis) is circumvented by bringing the tube out extraperitoneally through a lateral stab wound I have therefore applied this technique to the fashioning of a terminal colostomy following an abdomino-perineal operation The descending colon, being still fixed in the lateral sulcus, is brought out extraperitoneally before passing through the other layers of the abdominal wall

The fashioning of these colostomies is technically easier if it is done before the closure of the new peritoneal floor Hæmostats are fixed to the edge of the peritoneum and the rectus sheath on the left-hand side of the wound The skin is gently held with the same tension A circle of skin about an inch in diameter is excised * at the normal site, together with a small

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* A simple wad-punch purchased from a gunsmith and honed to a fine edge makes an excellent circular knife for cutting the skin and deeper tissues The diameter should be one inch for colostomy and seven-eighths of an inch for ileostomy If the skin is unusually tough the edge of the wad punch may be supported gently by a block of wood held within the abdomen while the punch is struck gently with a mallet

amount of fat and aponeurosis of the external oblique The internal oblique and transversus muscle are split in the line of their fibres, but care is taken *not* to pass through the peritoneum With the finger a track is burrowed around the outside of the peritoneum to the raw surface posteriorly where the descending colon is taking attachment Along this track the terminal bowel, previously crushed and divided, is guided by means of a large pair of Duval's forceps The peritoneal floor is then closed in the usual way, and the colostomy is sutured to the skin margin with interrupted cotton sutures, as suggested by Hermon Taylor and described by Butler[1]

Care should be taken that there is no kinking of any residual mobile sigmoid, between the lower end of the descending colon and the point where it begins to tunnel away beneath the peritoneum If there is a tendency to kinking, it is well to pull more of the sigmoid through until the descending colon lies comfortably Occasionally a number of interrupted sutures may be required just where the descending colon tunnels a way in its new extraperitoneal course

Of late I have used the same method for creating a terminal ileostomy In this operation, the lie of the mesentery may call for a little ingenuity

I have found this procedure much easier than attempts to close the lateral space in the manner usually practised

Preliminary Communication

MAMMOTROPHIC HORMONE IN SERUM OF HEALTHY WOMEN

THE urine of healthy women contains a hormone which induces a specific growth response in the rudimentary mammary glands of weanling male mice[2,3] This hormone is probably not an œstrogenic steroid, and the results of a series of experiments in which female urine was injected into hypophysectomised weanling males suggest that it is produced by the anterior pituitary[4]

In this communication experiments are recorded in which the blood-serum of five normal premenopausal women, together with œstrone and progesterone, was injected into totally hypophysectomised weanling male mice The results leave little doubt that a mammotrophic agent is present in recognisable amounts in the serum of healthy women, and afford further evidence that it is produced by the anterior pituitary

METHODS

Totally hypophysectomised weanling male mice, of the reactive Strong A_2G strain, bred under strict supervision in our own laboratories, were used in all experiments The sella turcica of each animal was serially sectioned at the end of each experiment Each sella yielded approximately 250 sections If anterior pituitary remnants were discovered the animal was discarded In approximately one animal in five hypophysectomy proved to have been incomplete Each animal was given, by subcutaneous injection, 0 1 ml of human premenopausal serum, together with 0 125 µg of œstrone and 0 75 mg of progesterone twice daily for five days

The mammary growth response was estimated by counting the number of large, deeply-staining, club-shaped swellings ("clubs") at the duct ends of the mammæ and calculating the mean number of clubs per gland No structure having a diameter less than twice that of its parent duct was counted as a club It has previously been shown[5] that the presence in significant numbers of cellular clubs of this size in the mammæ of weanling males of the Strong A_2G strain is a clear indication of a growth response induced by an artificial and specific exogenous mammary stimulus

During the past eighteen months, including the period covered by the experiments reported here, the mean number of large clubs per gland in the mammæ of untreated, intact weanling male mice of the age and strain used in these experiments has been estimated at regular intervals This figure has been invariably less than 1 0, and over an adequate recent period has shown a range of 0 75 to 0 05 with a mean of 0 5

RESULTS AND DISCUSSION

The accompanying table shows the intensity of the mammary growth response induced by the serum obtained from five healthy premenopausal women in the second half of the menstrual cycle

RESPONSE OF HYPOPHYSECTOMISED MICE TO SERUM OF FIVE HEALTHY PREMENOPAUSAL WOMEN

Serum no	Total no of hypophysectomised mice	Total no of mammary glands examined	Total no of clubs	Mammary growth response (clubs per gland*)
1	6	34	123	3 5
2	11	65	128	2 0
3	10	59	365	6 2
4	9	53	213	4 0
5	10	58	267	4 6

* Untreated intact controls have 0 5 clubs per gland

There is convincing experimental evidence that the administration of an œstrogenic steroid and progesterone to the hypophysectomised small mammal is powerless to induce a significant mammary growth response, providing that the hypophysectomy is proved to be complete by serially sectioning the sella[6] We have previously shown this to be true of hypophysectomised Strong A_2G weanling male mice, and this experiment was repeated with negative results during the time the work now reported was in progress A similar negative result was obtained when totally hypophysectomised weanling males were given prolactin alone over a period of five days

On the other hand, we have been impressed by the vigour of the mammary reactions observed in animals of these control groups in which a relatively small and insignificant fragment of anterior pituitary was left behind, more especially if the fragment contained cells whose cytoplasm was eosinophilic

Prolactin + œstrogen + progesterone invariably induces a mammary growth response in the totally hypophysectomised small mammal, and at optimal dose levels in reactive A_2G male weanlings this response is often spectacular To eliminate the possibility in the experiments reported that the mice injected with human serum were in a non-reactive phase, we have controlled each experiment in which human serum + œstrone + progesterone were given by setting up, at the same time, a group of totally hypophysectomised weanlings which were given prolactin + œstrone + progesterone A satisfactory mammary growth response was induced in all such controls and a similar but less intense response was obtained in all animals when human female serum was substituted for the prolactin of this hormone combination

The quantitative extraction of the mammotrophic hormone from serum is likely to prove far more accurate than its extraction from urine The above results, when amplified and confirmed, may therefore provide the necessary basic information for devising a reasonably accurate method for the bioassay of mammotrophic hormone in human serum

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[1] Butler, E C B *Proc R Soc Med* 1952, 45, 41
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CONCLUSIONS

A mammotrophic hormone has been found in the serum of five healthy premenopausal women

The experiments used for the identification of this hormone were designed also to provide information on the site of its production

They suggest that it is produced by the anterior pituitary

The Armour Laboratories, Kankakee, U S.A , kindly supplied the sample of prolactin used in these experiments, 1 mg contains 21 8 international units of prolactin by pigeon-crop assay The preparation has not been assayed for growth hormone We have evidence, however, that it contains a small but biologically active amount of this hormone.[3]

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New Inventions

MODIFIED TRACHEOTOMY TUBE

TRACHEOTOMY has been advocated for acute respiratory embarrassment in many conditions, both medical and surgical Except for repeated bronchoscopy, it is the method of choice in keeping the large bronchi clear of secretions, for all that is required is the passage of a catheter through the tracheostoma Unfortunately, the accumulation of secretions within the smaller branches of the bronchial tree cannot be reached by means of a catheter, and so may give rise to small areas of atelectasis, infection, and bronchopneumonia So that the smaller divisions of the bronchial tree may be cleared effectively, the secretions must be coughed up into the larger bronchi They may then be removed by means of a catheter Patients with tracheostomies, however, cannot cough effectively because they cannot build up the requisite intrathoracic pressure, since the larynx is partly deprived of its natural function In the conscious adult this disadvantage may be obviated by asking him to inspire, when coughing may then be made effective by occlusion of the tracheostomy But smaller children, and especially infants, will seldom cooperate in this manner Even if they do, the respiratory rate is much higher and it is difficult to correlate occlusion of the tracheostoma with the inspiratory and explosive efforts of the child Occlusion of the tracheostoma at the wrong time will cause a feeling of suffocation, and the increased negative pressure in the alveoli may cause further alveolar collapse

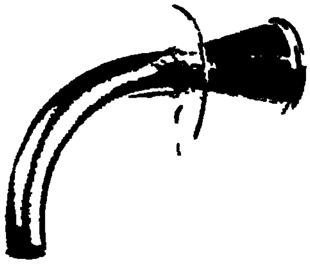
Fig 1—Inner tube

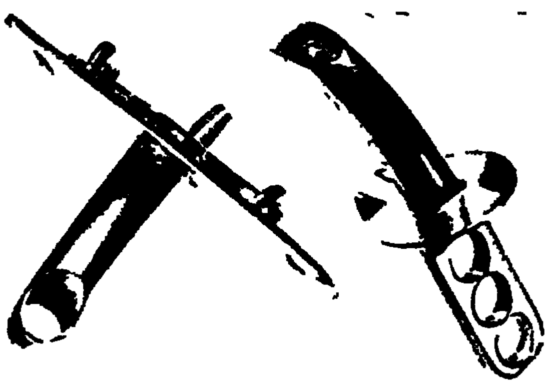
Fig 2—Outer tube and occluder

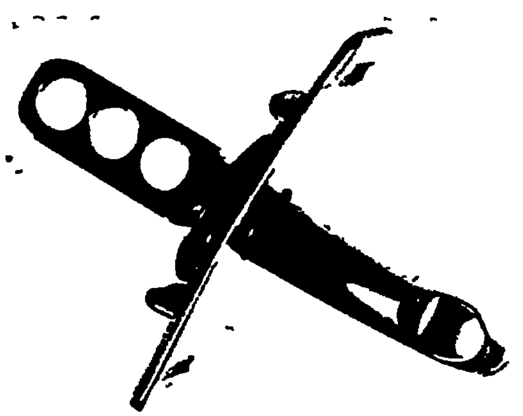
Fig 3—Occluder in position in outer tube, showing restoration of anatomical airway

With the above factors in mind, it was decided to modify the tracheotomy tubes in present use The Alder Hey tube consists of an introducer, outer and inner tubes, and an occluder The introducer requires no description, being similar to the standard pattern The inner tube (fig 1) also resembles the standard pattern, and consists of a hollow curved metal cylinder open at both ends The superior end of this tube, however, is drawn out to a diameter much wider than the part which rests in the trachea The outer tube (fig 2) differs in that a hole has been bored on the superior aspect so that it lies in direct line with the aperture in the lower end of the tube. The occluder (fig 2) is a solid metal cylinder, and fits in the outer tube when the inner tube has been removed

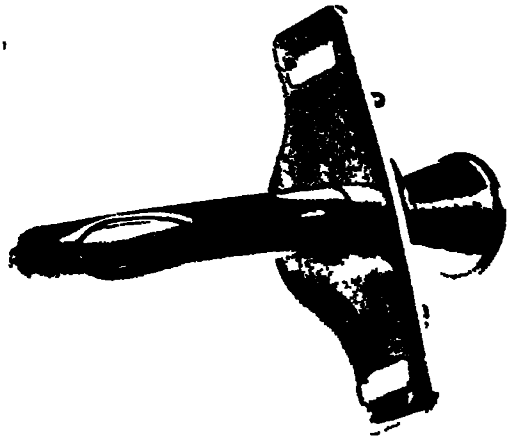
Fig 4—Inner tube lying within outer tube

The occluder, when inserted, restores the normal anatomical airway (fig 3) If the child is trying to cough, either spontaneously or after stimulation by a catheter, the inner tube may be quickly removed and the occluder inserted The normal airway being thus restored, coughing will be instantly effective, provided the laryngeal orifice is not completely occluded Any sputum produced may then be expectorated through the normal channels or collected from the larger bronchi by means of a catheter, on removal of the occluder The inner tube may then be replaced (fig 4) This method therefore has the advantage of restoring the normal anatomical airway, which may again be converted into a tracheotomy in a few seconds Any secretions collecting from the pharynx above the tube will also be expectorated, and the danger of their running down alongside the tracheotomy tube will be reduced without the unpleasantness of repetitive pharyngeal suction The aperture in the inner tube has been so placed that any attempt to cough will be as forceful as possible There is no danger of interstitial emphysema or loss of power in coughing resulting from leakage as there is if the tracheotomy tube is bifid along the entire length The occluder may of course be inserted when weaning from respiration through a tracheostoma to that through the natural airway If for any reason an anæsthetic is required with the usual tracheotomy apparatus, a cutdown endotracheal tube has to be inserted into the inner tube In a child this considerably reduces the lumen of the inner tube, which is already small In the Alder Hey tracheotomy tube the end is expanded so that the anæsthetic tubing may be directly connected with no danger of reduction of the diameter of the airway

This type of tracheotomy tube may be especially useful in tracheobronchitis, pneumonia, stove-in-chest injuries, and after chest operations

The tube may be obtained for children or adults from Elliots Scientific Instruments, Ltd , Buckland Street, Liverpool, 17

I wish to thank Mr A Rutana, registrar in ear, nose, and throat surgery at Alder Hey Children's Hospital, Liverpool, for allowing me to use this tube in his patients, and for his kind advice and criticism My thanks are due to Mr F T Howells of Elliots Limited, who made this tube to my specification, and to Mr Rodney R Green, photographer to Alder Hey Children's Hospital, who took the photographs

Alder Hey Children's Hospital,
Liverpool

FRANK WILSON
M B Lond , F F A R C S , D A

Reviews of Books

My Life with the Microbes

SELMAN A WAKSMAN, PH D , director, Institute of Microbiology, Rutgers University London Robert Hale 1958 Pp 320 21*s*

THIS is the autobiography of the scientist who has earned himself a place in history by his discovery, in September, 1943, of streptomycin—the first antibiotic shown to be of value in the treatment of tuberculosis He is less widely known as the originator of that useful addition to our vocabulary, "antibiotic"

He was born in 1888, in a small township in the Russian Ukraine He prepared himself for the entrance examination of Odessa University, but met on all sides such discrimination against Jewish students that, at the age of 22, he resolved to quit the Old World for the New He joined some distant relatives in Philadelphia, and then entered Rutgers University to study for an agricultural degree

Within a few years the new science of soil microbiology attracted his interest, and to it he has since devoted his life His first monograph was concerned with the characteristics of a little-known group of microorganisms, which resemble both bacteria and fungi in some features, but which are, in fact, distinct from both—the actinomycetes Eighteen years later it was from cultures of one of these organisms that streptomycin was isolated—not as the result of a single stroke of good fortune, but as the logical outcome of a carefully devised, tedious, and painstaking piece of research

His enthusiasm for his subject shines throughout his book One consequence may be that it will appeal more to the bacteriologist and laboratory worker than to the clinician, but every doctor can read with interest of the steps by which an impecunious immigrant in a strange land, with scarcely enough English to make himself understood, became one of America's most notable scientists

Cerebral Palsy in Childhood

GRACE E WOODS, M D , deputy medical superintendent, Hortham Hospital Bristol John Wright 1957 Pp 154 27*s* 6*d*

SEVERAL books on this subject have lately appeared, and this, the elaboration of an M D thesis, is an outstanding one It is notable for the precision of its text, and clinical description and examination are particularly clearly set out Unusual terminology is avoided , indeed, quite ordinary abbreviations are translated at the beginning

The patients described came from a circumscribed area of England and they were mainly over the age of 5 years The six principal clinical groups of cerebral palsy are effectively described , and ætiology as well as probable physical disability are summarised Dr Woods does not stop there, however, and she goes very fully into possible defects of special senses

There is no attempt to discuss treatment or education, but the description of the assessment of educability is clear and will be a help to others interested in the vital matter of cerebral palsy, which affected 1 9 per 1000 live births attaining the age of 5 years in Bristol during the past decade

Methods in Surgical Pathology

HENRY A TELOH, M D , assistant professor of pathology, North-Western University Medical School, Chicago, Ill Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 127 36*s*

INTENDED for the trainee in pathology, this book is a detailed guide to the naked-eye inspection of surgical specimens in the laboratory and the preparation of blocks for diagnostic histological examination Emphasis is laid on providing the surgeon with useful and prompt information, and methods of dealing with various surgical specimens are given systematically in 28 chapters Other chapters deal with more general topics, including operating-room techniques, tissue bacteriology, and prognosis The author recommends the pathologist to prepare frozen sections personally, and gives two of his own techniques Not all morbid histologists may agree with Dr Teloh that careful naked-eye examination of specimens is often more satisfactory than examining frozen sections In this country trainees are now unlikely to be asked to prepare blocks for section from surgical specimens without first being instructed by demonstration, followed by constant supervision of this important task, but personal teaching by experienced pathologists would be effectively supplemented by this book An appendix sets out in detail some illustrative reports, including histology and diagnosis

The book should be read by all pathologists in training, and it will also interest surgeons who wish to learn about the methods of examining excised specimens

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Fossil Men (London Thames & Hudson 1957 Pp 535 84*s*)—The fourth French *edition of the* world-renowned textbook of human palæontology by Prof Marcellin Boule and Prof Henri Vallois is here well translated by Michael Bullock in almost impeccable English, well subedited, and profusely and intelligently illustrated to tell the story of discoveries of fossil bones and implements of primitive man throughout the inhabited world In his introduction Dr Kenneth Oakley says that it is "the most comprehensive and authoritative general work on human palæontology" and tells us that Professor Boule "was originally one of the strongest opponents of the view that the Piltdown jawbone belonged to the same creature as the human braincase," and that Professor Vallois is "the leading exponent" of the view that "primitive *Homo sapiens* came into existence during Middle Pleistocene times, and evolved independently but parallel to the Neanderthal type"

Metabolism of the Nervous System (London Pergamon Press 1957 Pp 581 £5)—Dr Derek Richter has edited the proceedings of the 2nd International Neurochemical Symposium, held in Denmark in 1956 Each section opened with a review, followed by several short papers The emphasis in 1956 was on the adult nervous system, and the relation of metabolism to structure and function Speakers attended from Europe, North America, the Soviet Union, and Japan

THE LANCET
LONDON 15 MARCH 1958

Suicide and the Law

One of the more archaic laws in this country is that by which attempted suicide is a criminal offence Scotland and most other countries seem content without such a law, and in France it was abolished as long ago as 1790

The origins of this local taboo, now reviewed by Prof Glanville Williams,[1] are not entirely creditable the inherent sinfulness of suicide seems to rest on shaky theological foundations, while its legal punishment originated largely in the convenience of making a suicide's property forfeit to the Crown Not only have there been other countries in which suicide has been approved, but there are also circumstances in which our own culture approves it. That Captain Oates should give up his life in the way he did was generally recognised as an act of courage, setting a fine example If the same criteria were applied to the depressive, his motives likewise might win respect; for he too believes that others will be better off without him

Law and custom have undergone many civilising changes since the public dishonouring of the corpse in the 17th century, but vestiges of an older time remain, notably among some of the representatives of Religion and Law Many attempts at suicide are not made known to the police, but in London at least the duty is still laid on ambulance men to notify all their cases, except those which have come to the notice of the patient's own doctor Where a serious injury has occurred it is reasonable for the police to satisfy themselves on the facts, but to put a disturbed patient on a charge (before or after treatment), or to place a constable by his bed, is not helpful Still less is it helpful to incarcerate the mentally ill in prison this seems to us the very worst way of bringing about the social rehabilitation that such patients need And there seems no doubt that would-be suicides committed to prison *are* mentally disturbed Dr Epps showed this in her study of 100 consecutive admissions of attempted suicides to Holloway Prison,[2] and we believe that her experiences are the rule rather than the exception Her important findings suggest, too, that the law does not work effectively as a deterrent, and we may note that Scotland (with no law against suicides) has only 45 suicides per million, compared with 79 in England[3] Could it be that unconscious mechanisms, such as resistance or desire for punishment, make suicide more likely where it is forbidden?

One of the most alarming aspects of this law is the irregularity with which it is applied Some police forces do not prosecute where there is any responsible relative or friend,[4] and local superintendents have remarkable powers of discretion in deciding whether or not to bring a charge In 1955, out of 5220 attempted suicides known to the police, 43 were imprisoned: the figures for 1956 are much the same. Williams asks pertinently what principles are used in selection, or whether this depends entirely on the idiosyncrasy of judge or magistrate[5] Perhaps the strongest argument for the existing law is that it obliges some recalcitrant cases to receive treatment, and Dr R I Milne,[6] a London coroner, has declared that medical treatment is aided, rather than hampered, by the activities of magistrates and police. Nevertheless it seems to us that, without the aid of criminal Law, most of the determined suicidal patients could be persuaded to enter hospital for treatment, and on the rare occasions where a patient cannot be so persuaded recourse can be had to mental certification Some compulsory powers are still needed, but these are much better related to the therapeutic services than to the punitive. It is surely significant that in the recent correspondence in *The Times*[7] no voice was raised decisively in defence of the present law In the House of Commons, Mr Butler, the Home Secretary, said he had no evidence that an alteration in the law would be acceptable to public opinion[8] *The Times*, however, believes that the public has no opinion,[9] and this seems to be largely true there is no general feeling about suicide comparable to that on, say, the death penalty or the punishment of sexual offences A motion tabled by Mr Kenneth Robinson on Feb 27—that suicide be removed from the category of criminal offences[10]—has scarcely added a ripple to the turbulent waters of Fleet Street

It seems clear that this outdated law is as inconsistent and inequitable in its application as it is damaging in its effects Its virtues are hard to discover its vices are blatant The sooner it is done away with the better

Precision and Prediction in Hæmophilia

Developments in technique are bringing quantitative precision to the exploration of blood-clotting defects in hæmophilia and related syndromes These quantitative estimates enable better forecasts to be made about the likelihood of severe bleeding, whether spontaneous, or following mild trauma, or after, say, dental extraction or tonsillectomy The methods used have also uncovered unexpected new facts, some of them difficult to explain It has long been known that if, in a hæmophilic patient, the blood-clotting time was thirty minutes or longer, the patient was liable to spontaneous hæmorrhages, hæmarthroses, and severe bleeding after trauma, but if the clotting-time was less than thirty minutes, even if only a little longer than normal, it could not be assumed that the patient would be only mildly affected and that, for example, a tooth could be extracted with minimal precautions A survey by Biggs and Macfarlane[11] of investigations of clotting function in 187 cases of hæmophilia and related syndromes contains much interesting information and reflects the present increasingly quantitative outlook

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[2] Epps, P *Lancet*, 1957, i, 182
[3] Williams, G *op cit* p 247
[4] Williams, G *op cit* p 249
[5] Williams, G *op cit* p 251
[6] *Times*, Feb 20 1958
[7] *ibid* Feb 11 20 21 24 25, 26 1958
[8] See *Lancet*, Feb 15 1958 p 354
[9] Leading article *Times* Feb 28 1958
[10] See *Lancet*, March 8 1958 p 519
[11] Biggs, R, Macfarlane, R G *Brit J Hæmat* 1958, 4 1

Classical hæmophilia is now " disintegrated into a number of distinct entities with a similar symptomatology ", BIGGS and MACFARLANE's group included 138 cases of hæmophilia, 20 of Christmas disease, and 3 of ROSENTHAL's[12] syndrome of deficiency of " plasma thromboplastin antecedent " (P T A), they also studied a few cases of other syndromes in which deficiency of antihæmophilic globulin had been found, including cases in 11 families with von Willebrand's disease In 115 of their hæmophilic patients they assayed quantitatively the deficiency of antihæmophilic globulin in the plasma

The techniques,[13] [14] which are not simple, are based on the thromboplastin-generation test This test uses (1) a plasma fraction treated with specially prepared aluminium hydroxide which absorbs prothrombin, Christmas factor, and factor VII, and leaves antihæmophilic globulin and factor V, (2) serum which contains Christmas factor and factor VII, and (3) a suspension of platelets When these three reagents are mixed and incubated at 37°C in the presence of ionised calcium, thromboplastin is formed, the amount of plasma-thromboplastin formed is estimated by adding some of the incubated mixture to a substrate of normal citrated plasma in the presence of calcium and observing the clotting-time—normally about ten seconds—of the substrate plasma In hæmophilia the alumina-plasma will be lacking in antihæmophilic globulin, so thromboplastin generation will be defective and the clotting-time of the substrate plasma will be prolonged By comparing the prolongation of the thromboplastin-generation test with a similar effect produced by diluting normal plasma, it is possible to estimate the diminution of antihæmophilic globulin in the hæmophilic patient's plasma as compared with normal plasma

BIGGS and MACFARLANE thus found that, of their 115 hæmophilic patients, 63 had no detectable antihæmophilic globulin at all, and the remaining 52 had various levels up to 49% of normal The group with no detectable antihæmophilic globulin included all except 1 of the severely affected patients in their series, and any patient with less than 10% needed blood-transfusion after tooth extraction or tonsillectomy BIGGS and MACFARLANE point out that " it is fairly safe to say that a patient who has had teeth extracted on two occasions without bleeding for more than one week or who has had an uneventful tonsillectomy is unlikely to have the mildest degree of hæmophilia " But 6 of their patients with between 15 and 48% antihæmophilic globulin did not need transfusion after tonsillectomy, though 1 with 22% and 1 with 25% had to be transfused They conclude that 5–10% antihæmophilic globulin protects against ordinary everyday stresses, but as much as 30–40% of normal is required to stop bleeding from major wounds or surgical operation sites, this involves giving a lot of blood[15] It is this sort of evidence that leads BIGGS and MACFARLANE to conclude that the severity of the hæmophilic defect is closely correlated with the blood level of antihæmophilic globulin, and that consequently the estimation of this level is of great value in prognosis and the control of treatment

In the other syndromes studied, quantitative methods have so far proved less clearly helpful In Christmas disease the factor is completely absent in all except the mildest cases, where the levels are 0–20% of normal In von Willebrand's disease the observed deficiency of antihæmophilic globulin in 8 patients varied from 1 6 to 26% of normal, and they had prolonged bleeding-times as well In ROSENTHAL's P T A deficiency there is the curious combination of prolonged clotting-time, an abnormal prothrombin-consumption test, but nearly normal results with the thromboplastin-generation test, the cases are too few yet for precise estimation—BIGGS and MACFARLANE had 3 in their series—nor is the clotting defect clear, though SHARP[16] has suggested that it is lack of " viscous metamorphosis of platelets " in the earliest stage of the clotting process

NOUR-ELDIN and WILKINSON[17] have set out evidence that another factor besides lack of antihæmophilic globulin or Christmas factor is linked with the severity of these diseases This factor is an anticoagulant which they have detected in the plasma of patients with hæmophilia or Christmas disease, and its presence appears to be part of the inherited clotting abnormality Using the current eponymous fashion, they call this factor " Bridge anticoagulant " after the first patient in whose plasma they detected it Bridge anticoagulant was found, and its activity estimated, by using a variation of the thromboplastin-generation test described above NOUR-ELDIN and WILKINSON found that if they used the patient's *own* citrated plasma as the test substrate, the clotting-time of the mixture was *longer* than when normal plasma was used This effect might have been attributed to the deficiency of antihæmophilic globulin in the patient's plasma, but when they compared the results of using undiluted plasma or plasma diluted 1 in 5 as a test substrate, they found that the clotting-times were *longer* with the *undiluted* than the diluted plasma—the reverse of what would have been expected if deficiency of antihæmophilic globulin was responsible for the effect The results could be explained by the presence of an anticoagulant, which would, of course, be less effective when diluted NOUR-ELDIN and WILKINSON have found this Bridge anticoagulant in the plasma of each of the 109 patients with hæmophilia and 14 with Christmas disease so far tested, the anticoagulant did not remain active in the *serum* The activity of Bridge anticoagulant can be estimated by the effect of prolonging the substrate clotting-times in the thromboplastin-generation test, the greater the difference between the clotting-times when normal and when patient's plasma is used as substrate, the greater the activity of the anticoagulant They found that the more active the anticoagulant, the severer the clinical manifestations of the disease

For example, a patient aged 32 had a whole-blood clotting-time of sixteen and a half minutes, he had had spontaneous bruising, melæna, epistaxes, and hæmarthroses, the thromboplastin-generation test substrate clotting-times using normal and his own undiluted plasmas were eighty-two and two hundred and four seconds respectively. Another patient, aged 10, had a clotting-time of nine and a half minutes, the substrate times with normal and with patient's plasmas were twenty-seven and thirty-three seconds, and this patient had no spontaneous hæmorrhages though he bled excessively after trauma.

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[12] Rosenthal R L, Dreskin, O H, Rosenthal, N *Blood*, 1955, 10, 120

[13] Biggs R., Macfarlane, R G Human Blood Coagulation *and its Disorders*, p 423 Oxford, 1957

[14] Biggs R *Lancet*, 1957, ii, 311

[15] *ibid* 1957, i, 376

[16] Sharp, A A *Brit J Hæmatol* 1958 4 28

[17] Nour-Eldin, F, Wilkinson, J F *ibid* p 38

Anticoagulants have been reported in hæmophilia before, notably by TOCANTINS[18] and his co-workers, but the properties of the Tocantins anticoagulant are quite different from those of Bridge anticoagulant, nor does Bridge anticoagulant link up with the type of change described by HOUGIE.[19] The Bridge anticoagulant does not fragment the hæmophilia syndrome, but actually provides a link between classical hæmophilia and Christmas disease. It will be very interesting to see whether it is found in other members of the hæmophilia syndrome; NOUR-ELDIN and WILKINSON hint that it is absent in von Willebrand's disease. Fortunately the activity of Bridge anticoagulant can be estimated by a slight variation of the technique used for estimating antihæmophilic-globulin deficiency. Neither test can be satisfactorily undertaken by the routine laboratory that has few of these patients to deal with. It is now all the more important to send patients with suspected hæmophilia, especially children, to one of the special units, because, with these tests, they can give a reasonably accurate answer to the anxious parents' question: Will my child be severely or mildly affected? The answer may well affect the arrangements for schooling and future occupation.

Occupation and Health

THE publication of the Registrar General's Supplement on Occupational Mortality is always an important event, and, because war prevented the conduct of the decennial Census due in 1941, the report on the experience of mortality by occupation in the five years 1949–53 has special interest. The pivotal Census years of 1931 and 1951 represent the pit of economic depression and the full development of a Welfare State. Between lies a social revolution which might be expected to have altered the relationships of the risk of death in the different strata of society. In the latest report,[20] as in its forerunners, the population is divided according to occupation, and these occupations are grouped, according to the levels of education and social standing rather than income, into the five social classes: I, professional, II, managerial, III, skilled, IV, semi-skilled, and V, unskilled. In 1931 the mortality experience of men in these five social classes was compared with that of their wives, so that risks specific to the husband's occupation could be isolated from any general effect on health of the social and domestic environment or habits which they have in common. The same technique has been followed in the 1951 Census, and the changes in the work pattern of married women give fresh point to the comparison of present and past experience.

The introduction to the latest report reflects a certain sobriety about the interpretation of death-rates by occupation as obtained by current methods:

> An excessive death-rate in a particular occupational group compared either with other men or with their own wives need not imply a specific occupational hazard. Men are drawn to certain jobs because they feel that they have the vigour to undertake them or because the jobs offer a sheltered environment for the less robust. After initial recruitment to the more arduous tasks in the community, the subsequent wastage of the weaker men leaves a more resilient group of survivors whose mortality experience reflects their superior physique rather than the stresses of their working environment. As a result, the prescribed practice of allocating a death to the last occupation of the deceased man, rather than to the occupation in which he has spent the bulk of his working life, leads to understatement of the hazard which the latter may present. On the other hand, particularly in industries such as mining where the specific mortal risks are well known, the informant at the time of death registration may not describe the deceased man as he was employed at the time of his death but according to his previous job—e.g., as a coalmine face worker. Again, both at census and at death, there is a tendency for men to describe themselves or others as employed on work with rather higher social prestige than the task actually performed: the fireman becomes a miner, the surface worker at the mine becomes a face worker, and so on. Because "promotion" effects of this type are present at both census and death the resultant errors in the death-rates by occupation may not be great, but the Registrar General refers to studies in the mining industry, carried out with his help and the cooperation of the National Coal Board at the London School of Hygiene and Tropical Medicine, which suggest that errors in job description and classification may be important in any detailed survey of death-rates in specific mining occupations.
>
> The mortality experience of men's wives gives some indication of the effects of the immediate domestic environment. Broad regional differences in living conditions are illuminated by comparisons of social-class death-rates in different regions of the country. But the incidental risks of an occupation—e.g., the opportunities for excessive drinking among bartenders—are less easily identified. All these sources of consistent bias must, as the Registrar General emphasises, be remembered in interpreting the death-rates by occupation set out in this report.

Perhaps the most striking divergence between the 1931 and 1951 periods is in the overall trend in social-class mortality. In 1931 the death-rate rose consistently with descent of the social scale from class I to class V; in 1951 the W-shaped distribution of these rates results from the greater relative improvement in social classes II and IV—i.e., the managerial class and semi-skilled workers. Some of this disparity may be due to slight changes in classification, and some adjustments made in the report suggest that the low rate in social class IV can be thus explained. The reversal of the positions of social classes I and II cannot, however, be similarly accounted for, and the new superiority of the managerial class is shared by their wives.

Of the individual causes of death which make up these social-class differences in total death-rates, some follow the 1931 trends by increasing steadily in frequency in both sexes from social class I to V—tuberculosis, syphilis, cancer of the stomach, bronchitis, and pneumonia. Cancer of the lung has a similar trend only for males; the trend is reversed in females. Of the other neoplastic diseases, cancer of the uterus and breast have the contrary trends with social class which are already familiar, while leukæmia mortality falls consistently from social class I to V A summary of the gains and losses in social classes I and II suggests that their relative position has been altered by an increased mortality in social class I from coronary-artery disease, tuberculosis, accidents, cancer, vascular lesions of the central nervous system, and chronic endocarditis and a relative decrease, largely in cancer and bronchitis, in social class II

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[18] Tocantins, L. M. *Blood*, 1954, 9, 281.

[19] Hougie, C. C. *J. clin. Path.* 1953, 6, 30.

[20] Registrar General's Decennial Supplement, England and Wales, 1951. Occupational Mortality. Part II. H.M. Stationery Office, 1958. 2 vols. £7 7s.

The detailed account of the social and occupational patterns of the various causes of death will doubtless form the pabulum of many future essays on social medicine From the *embarras de richesse* purveyed in two large (and rather expensive) volumes, some biased sampling produces data of interest in more than one disease The changing epidemiological behaviour of coronary-artery disease, for example, has excited much controversy on the role in its ætiology of diet, exercise, smoking, and stress The continuing increase in the reported death-rate is unlikely to be entirely due to increasing diagnostic skill or changes in classification, and there is some consistency between the 1931 and 1951 Census in the male social-class gradient from its peak in the professional group The low death-rates from coronary-artery disease among the manual workers in the population would fit in with the idea that physical exercise is a powerful prophylactic against this disease In married women aged 20–64, on the other hand, the highest rates are among the wives of the manual workers Indeed the pre-war social gradient of mortality in both sexes which was compatible with the dietary-excess theory of causation has now been upset by this reversal in women Psychological explanations of coronary-artery disease may be somewhat under a cloud, but there is perhaps food for thought in the observation that, while the excessive death-rate early in life among senior Civil Servants may be part of the price of a Welfare State, occupational opportunities for exercise have not prevented the small group of professional cricketers, footballers, golfers, &c, from having a standardised mortality ratio 73% above the national average

An interest in the experience of our own profession need not be dismissed as mere hypochrondriasis Among the 34,000 medical practitioners alive about the time of the Census there were reported 1008 deaths instead of the 1129 expected at the rates for all males This gives a standardised mortality ratio of 89, which is less than the ratio of 106 reported for 1930–36 The introduction of the National Health Service thus does not seem to have been associated in time with an excessive mortality from all causes Doctors certainly have a standardised mortality ratio from coronary-artery disease of 159, but this differs little from the ratio of 152 for ministers of religion and not greatly from the value of 120 for dentists and 121 for members of the legal profession In the same way, although medical practitioners have an excessive number of deaths from poliomyelitis, this excess is equally evident among judges, barristers, and solicitors Of the remaining causes of death, only leukæmia, vascular lesions of the central nervous system, d suicide are much above the national average

In this report there are countless intriguing indications for further research in both occupational and general medicine Even if only a few such clues are successfully followed up, the General Register Office will not have laboured in vain

Lord of Misrule

ACADEMIC apathy is a complaint that is often flung at the students of today, but the words cannot justly be applied to the lively proceedings at Glasgow last month In the Scottish universities the election of a lord rector, the official representative of the student body, is often a vigorous affair, and his installation is an occasion when both licence and toleration are traditionally exercised But it is unusual for a Minister of the Crown and university and civic dignitaries to have to withdraw from the platform, bearing on their persons and gowns the unmistakable traces of unorthodox if misdirected missiles The press who had come to record the words of the Secretary of State for Home Affairs remained to report the students' exertions, which next morning were the subject of conversation in tube, bus, and train and of a leader in *The Times* Nobody could say that the students had, or deserved, a good press, but the feeling gradually gained ground that the incident was better left to academic and local reprimand than dealt with by national ukase

Nevertheless, the general question of student turbulence, why it persists, and whether it should, is of interest to us all At Glasgow the outbreak was aggravated by extraneous circumstances—the similar occasion at Edinburgh the day before, the Rochdale by-election, and the political personality of the new rector—but the episode is not an isolated one The Scottish universities, perhaps because of their long association with the universities of the Continent, have retained most firmly the medieval tradition of festivals of acknowledged horseplay at which the sway of the Lord of Misrule is, by some reluctantly, accepted But even south of the Border students have not entirely discarded these practices, and some, within the last few weeks, have rudely interrupted the performance of a pantomime These incidents are more likely to disturb, inconvenience, and annoy other people, and thus achieve publicity, in large cities where the university is a small part of the community But in the comparative privacy of the more secluded universities students have been known, though admittedly with less disturbance to the town, to use the calm of their cloisters for rites which form no part of the courses of study arranged for them

To understand, though not necessarily to support, these bouts of unreason and physical activity, we must consider the peculiar difficulties of the student His life, like so many other lives, is not easy Most of these young people are working hard, for today the student who does not pass his examinations does not remain at the university, and in every faculty the curriculum grows no lighter Most of them are fairly hard up and many of them add jobs in the vacation to term-time studies More important perhaps, their entrance into workaday life has been delayed They see many of their contemporaries started on their careers, earning money, and assuming adult responsibilities, while they still live in a state of semi-tutelage and semi-responsibility, still dependent on others—whether parents or State—for their board, keep, and pocket-money To stand on the brink of a swimming-pool, or of life, is a jittery business, especially if you are not yet sure how well you can swim; and something of the tension of these uncertain strenuous years has been shown in the reports of the student health services[1] Its occasional release, even though sometimes over-violent, is usually well tolerated, and the pleasantest part of the Glasgow ceremony was Mr **BUTLER**'s ready assumption of his new duties as lord rector and his championship of his new constituents

But these young people are the selected brains, and brawn, of the country They have surmounted every educational hurdle from the 11— onwards, and it is surely not beyond their wit to modify old customs and to find opportunities for robust relaxation which will not injure other people or their property Their fellow citizens, for instance, would have nothing but amused admiration for any good-tempered masquerade or well-planned exploit such as the visit of a party of unusual European royalty to a London hospital sports ground.[2] If the Lord of Misrule is to retain his place on the staff of the university health services, it is time for him to exchange his cap and bells for his thinking-cap and to devise new forms of therapy for his subjects

Annotations

NEW SOURCES OF FOOD

HALF the world is underfed, and the population still increases faster than its food-supply Temporary surpluses in a few favoured countries should not mask the real world shortage, for the disparity between the better-fed and the worse-fed nations is actually widening Mr N W Pirie, F.R.S., made these points in the lecture he was giving to the Royal Society of Arts last Wednesday,[3] and outlined means of producing more food—especially protein. In the past, production was increased largely by cultivating virgin lands, but none of those remaining are comparable to the areas opened up in the 19th century We could raise the output per acre (1) by improving the breed of plants, (2) by supplying more light, heat, and water (here cheap nuclear power may help, though it creates its own problems) and (3), more profitably, by using more fertilisers, especially in South and East Asia But Mr Pirie devoted most of his attention to prevention of waste

This involves not only the control of diseases and pests, and making use of material now rejected but also the avoidance of losses on conversion At present we use animals for conversion (i e of fodder to human food) and as a source of protein, though the animal adds nothing new and yields foodstuffs equivalent to only part of the vegetation it eats The merits of the animal are (1) that it provides a bigger ratio of protein to carbohydrate than does its fodder, (2) that the aminoacid composition of its protein is closer than that of some plants to what we believe suitable for man, (3) that it sometimes thrives on foods too fibrous for man, and (4) that animal foods are familiar and appeal to the palate At Rothamsted Experimental Station, where Mr Pirie is head of the biochemistry department, mechanical and chemical processes are being investigated which will separate from green leaves a substantial proportion of protein and other food elements direct, without using an animal as an intermediary At present the separation is incomplete, and some protein remains in a fibrous residue which is used as fodder for animals, but in the future this residue might be less wastefully subjected to conversion by microorganisms than by animals Useful enzymes (e g, that convert cellulose to glucose) abound in Nature and might be pressed into man's service. Moreover, of hundreds of thousands of plant species known, only about a hundred at present contribute significantly to human nutrition. "Our choice is still restricted unreasonably by the whims and limitations of primitive man" We should be searching the plant kingdom for species which will grow exuberantly and which contain nutritionally useful components which new techniques would enable us to extract. Research on these lines is especially appropriate for Britain, where we have little land but much scientific and technical skill

POSTOPERATIVE HYPOTENSION

HYPOTENSION in the postoperative period has been investigated by Barbour and Little[1] in close on 5500 patients Taking a systolic pressure of 90 mm. Hg or less in a normotensive patient, and a fall of 40–60 mm Hg in a hypertensive patient, as the criteria of an abnormally low pressure, they found that 1 in every 31 patients had a hypotensive episode

No-one should doubt the potential dangers of a drop in blood-pressure at this time Damage to the brain, perhaps discovered only at a later date from minor alterations in mental performance, death from sudden cardiac decompensation, and renal damage are recognised sequels, while vascular thrombosis and pulmonary embolism may in some measure be attributable to it Elderly and ill patients are most likely to suffer ill effects if the blood-pressure falls, but those who are otherwise fit may suffer when unrecognised slight hypotension is accentuated by the sitting position or an unnecessarily large dose of a sedative drug

The relationship between complications, early or late, and hypotension is unknown, routine recording of the blood-pressure immediately after operation is not common practice Considering the immense amount of skill, care, and time nowadays given to each patient by a team of highly specialised people in the operating-theatre, it seems illogical that soon afterwards, at a time often of rapid physiological transition, the patient should be transported to another part of the hospital, and there though observed for gross complications, rarely tested for the earliest premonitory signs

Barbour and Little divide the causes in their series into six main groups—cardiovascular, respiratory, pharmacological, neurogenic, hæmatological, and humoral The common causes include myocardial insufficiency from heart-disease, circulatory depression due to high blood-carbon-dioxide tension, associated with inadequate ventilation during anæsthesia, the effects of drugs, some of which exert their effect for many hours, and inadequately relieved pain. Occasionally the cause is less obvious, as when oligæmia from unobserved blood-loss during operation leads to postoperative hypotension (about 1500 ml. of blood can be lost during general anæsthesia without obvious change in the blood-pressure or pulse-rate[2]) or when a simple faint is precipitated by postural changes in a patient who has recently come round from an anæsthetic.[3] Quite severe hypotension may follow an operation and anæsthetic when the patient does not respond by the normal output of adrenocortical hormones, owing perhaps to previous treatment with cortisone or related steroids,[4] or perhaps to adrenal exhaustion after long or severe illness.

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[1] Parnell, R. W. *Lancet*, 1951, i, 731 Malleson, N. *ibid* 1954, i, 524

[2] [illegible] correspondence, *ibid* 1956, i, 346

[3] To be published in the journal of the society 6 John Adam Street Adelphi, London W.C.2

[1] Barbour, C. M., Little, D. M., Jr *J. Amer. med. Ass.* 1957, 165, 1529

This investigation by Barbour and Little shows both that significant postoperative hypotension is relatively common, and that the patient should be kept near those who, from their knowledge of his behaviour during the operation and anæsthesia, can easily recognise changes in the recovery period. All of their patients were observed in a recovery-room, and most of those who were hypotensive needed blood-transfusion.

RE-STENOSIS AFTER VALVOTOMY

FIFTY-SIX years ago Lauder Brunton[5] first suggested the surgical treatment of mitral stenosis by "elongating the natural opening", and at the time we expressed misgiving that[6] "the incision in such a valve would show a great tendency to unite directly and the state of the valve would then be worse than before." This doubt has hardly been confirmed in the ten years since mitral valvotomy was established. It might seem that fracturing or splitting the deformed valve must inevitably leave ragged, raw edges, inviting readherence of the cusps with subsequent stenosis matching the original in severity. Magarey[7] predicted that stenosis would recur after valvotomy because of thrombus formation on the irregular cusps, but Glover[8] has denied that it does. It is now evident that re-stenosis can take place in certain circumstances, but it is surprisingly uncommon. Belcher[9] has investigated its mechanism in eleven published cases and twelve of his own.

In all these cases improvement after the original valvotomy was not maintained, and at a second operation or necropsy refusion of the cusps was found. Belcher's findings suggest that the mobilisation of the valve cusps at operation is the crucial factor, and he emphasises that re-stenosis has not yet been seen where both commissures have been completely divided. In the majority of his own patients who needed a second operation, the valve had not originally been split beyond the critical areas of tendon insertion. These findings endorse the views of Brock,[10] who first emphasised the significance of the insertion of the main chordæ tendineæ. At these two sites, on either side of the central pathway of the mitral valve, the cusps are held most tightly in apposition during systole, and in Brock's view rheumatic adhesion first appears there; he termed them the critical areas of tendon insertion. The ideal valvotomy consists in division through these critical areas on each side, followed by splitting of the commissures to their lateral edges. In addition, the chordæ must be carefully separated from one another, and from the valve cusps, to ensure a maximum mobility. The pliancy of a valve[11] can often be deduced from auscultation, but until the heart is opened it is impossible to be certain how much can be achieved. fibrosis and calcification of the cusps, or fusion of the chordæ, may prevent more than slight separation, rendering the condition virtually inoperable; re-stenosis is likely to follow, even though some initial benefit is experienced. But if a calcified valve is suspected before operation, it does not follow that valvotomy is impossible. It is worth emphasising that a technically successful operation leads to disappearance, or shortening of the murmur and a softer first sound.[12]

Smouldering rheumatic activity is invariably difficult to confirm, and how often re-stenosis is due to this is uncertain. Belcher thinks that when re-stenosis follows complete separation of the commissures it may be the result of rheumatic activity, and in 7 published cases of this type rheumatism could be blamed in 5. After a technically imperfect valvotomy readherence may quickly result from fibrin deposition alone.[7] It is clear that successful valvotomy depends at least partly on proper appreciation of the anatomy and pathology of mitral stenosis, and Glover et al.[13] have said: "it must be the pathological changes in the valve and not the surgeon's ignorance of an ideal valvotomy which limits the operative procedure."

HEREDITY IN ENURESIS

IT is not always clear at just what point an extensive family study of a particular clinical condition becomes worth while. Patients with enuresis may well be heterogeneous; suggested causes of the condition range from anatomical defects of the upper urethra to psychological immaturity. A family study might be expected to indicate whether there is an appreciable genetic element in causation, perhaps to isolate a small proportion of cases with strong genetic determination, and, more generally, to reveal subvarieties of the condition by the fact that these breed true within families—though the alternative, non-genetic, explanation—that any familial concentration is due to a family tradition—must always be borne in mind.

The tendency for bed-wetting to occur in families has been known at least since the end of the last century. Obviously the proportion of a series of patients who are found to have a relation of some degree or other affected will depend on how thoroughly the family is investigated, and estimates of the proportion of patients with a positive family history vary from 3% to more than 90%. Blomfield and Douglas[14] in 1956, with a near-perfect sample of English children, found that significantly more brothers and sisters of regular bed-wetters were also affected than were the brothers and sisters of children who were dry at night—10·6% compared with 5·1%. The family inquiry was made by health visitors with no special training in taking family histories, but the series is a very large one and the relative findings are acceptable. Dr. Bertil Hallgren,[15] of Stockholm, has re-examined this question in an admirably thorough survey in which he personally examined children and questioned their parents Index cases were collected from the psychiatric department of two children's hospitals in Stockholm—111 patients from one hospital and 119 from the other The series was probably somewhat selected for high frequency and late age at cessation of bed-wetting, and for persistent emotional disturbances, on the other hand, mentally backward children were probably under-represented In about 15% of patients the enuresis was "acquired", in the sense that control had been gained and then lost again There is good reason to suppose that anatomical defects play little part in the causation of the abnormality in such children Of the 119 children from one hospital 105 were examined by urethrocystography and 20 in whom further investigation seemed desirable underwent cystoscopy Of these, 3 had minor anatomical abnormalities, which were treated without affecting the enuresis

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[2] de Wardener, H. E., Miles, B. E., Lee, G. de J., Churchill-Davidson, H. C., Wylie, W. D., Sharpey-Schafer, E. P. *Clin. Sci.* 1953, 12, 175.

[3] Bourne, J. G. *Lancet*, 1957, ii, 499.

[4] Salassa, R. M., Bennett, W. A., Keating, F. R., jr., Sprague, R. G. *J. Amer. med. Ass.* 1953, 132, 1509.

[5] Brunton, L. *Lancet*, 1902, i, 352.

[6] *ibid.* p. 461.

[7] Magarey, F. R. *Brit. med. J.* 1951, i, 856.

[8] Glover, R. P. *Trans. Amer. Coll. Cardiol.* 1955, 5, 209.

[9] Belcher, J. R. *Brit. Heart J.* 1958, 20, 76.

[10] Brock, R. C. *ibid.* 1952, 14, 489.

[11] Sellors, T. H., Bedford, D. E., Somerville, W. *Brit. med. J.* 1953, ii, 1059.

[12] Wood, P. Diseases of the Heart and Circulation. London.

[13] Glover, R. P., Davila, J. C., O'Neill, T. J. E., Janton, O. H. *Circulation*, 1955, 11, 14.

[14] Blomfield, J. M., Douglas, J. W. B. *Lancet*, 1956, ii, 850.

[15] Hallgren, B. *Acta psychiat. Kbh.* 1957, 32, suppl. 114.

Hallgren finds that the family analysis does not distinguish between the two main clinical groupings—"nocturnal" enuresis and "nocturnal plus diurnal" enuresis Any genetic predisposition is therefore common to both conditions The data suggest that the family risks are higher for primary than for acquired enuresis, the difference is significant for the parents but not for the relatively few brothers and sisters Grouping primary and acquired cases together the risks to parents and brothers and sisters is clearly higher than for the general population Hallgren estimates the risks in the general population of Stockholm as 10% for nocturnal enuresis and 2% for nocturnal plus diurnal enuresis in boys, while for girls it is 6% and 2% respectively He found that of 208 fathers 64 (33%) had been affected, and, assuming ascertainment by individual, of 129 brothers 40 (31%) had been or were affected, he also found that of 215 mothers 38 (18%) and of 133 sisters 25 (19%) had been affected These proportions are between two and three times that in the general population In the nine families where both parents had been affected, 7 of 10 siblings were also affected

Genetic predisposition is perhaps likely to account for a greater proportion of this family resemblance than family tradition A large twin study would help to establish the distinction The nature of the genetic predisposition remains unclear The reality of the other element—family tradition—is shown in Blomfield and Douglas' finding that bed-wetting is more prevalent in the lower social classes, and in urban than in rural children

PROSPECTS IN THE PREVENTION OF BLINDNESS

THE comprehensive welfare services for the blind in this country have yielded much statistical information Sorsby's reports[1–3] have been supplemented by his summaries in the annual reports of the chief medical officer of the Ministry of Health[4] An outstanding problem revealed by these studies was the high proportion of cataract patients—about 25%—amongst those registered as blind Some 80% of those registered as blind from cataract had not sought or obtained treatment. In 1954 the Ministry of Health made available more beds for cataract patients and sought to distribute the waiting-lists more evenly[5], and now it has issued a direct appeal to general practitioners, who in the first place have charge of the potential cataract patient A widely distributed memorandum[6] points out that the old teaching that operation could not be undertaken until the cataract was ripe is no longer valid, for by modern methods the cataract can be removed as soon as vision is seriously reduced One difficulty is that no less than a third of new registrations of blindness relate to people over the age of 80, and, though cataract surgery at such an advanced age generally presents no special problems, in many patients operation might have been undertaken under better conditions at an earlier age It is disturbing that, in spite of the general medical services available to all under the National Health Service and the recent expansion of ophthalmic departments, most of those seeking admission to the Blind Register apply through the National Assistance Board, and not through medical agencies

Cataract is generally regarded as a "senile" affection, and so are the macular lesions misnamed senile macular degeneration Together these two affections account for nearly 50% of all registrations of blindness But out of altogether nearly 5 million aged over 65 years only some several thousands a year are affected by these lesions, the Ministry's memorandum rightly emphasises that old age by itself does not cause blindness, and the nature of these two affections is unknown Little is known, either, of glaucoma, another major cause of blindness, which tends to affect younger patients Though much can be hoped for from administrative action on cataract, there is little immediate prospect of reducing the incidence of blindness from senile macular degeneration or from glaucoma, but early diagnosis and treatment are essential in the management of glaucoma[7]

Overall surveys—because of the high proportion of aged among the newly registered—necessarily emphasise cataract, senile macular degeneration, and glaucoma A different picture emerges if attention is confined to the blind under the age of 50 Here optic atrophy stands out as the largest single group, with 22 6% of the total in 1955 and 23 0% in 1956, and among the specified causes of optic atrophy "pre-natal influences", intracranial lesions, and disseminated sclerosis were outstanding with a total of 65 8%, while in some 18% no cause was established Optic atrophy therefore calls for urgent investigation if the amount of blindness in the age-groups under 50 is to be substantially diminished Retinitis pigmentosa and its allied conditions, myopia, congenital defects, diabetic retinopathy, and iritis and iridocyclitis all account for a substantial quota of cases

Any survey of the causes of blindness today shows that there are one major surgical problem—cataract—and a mass of medical problems Traditionally ophthalmology is largely a surgical specialty, and the recognition that a substantial series of medical problems lie before it is in itself a considerable advance Today the general practitioner is being urged to select his cases for surgical treatment, but he may be called on to play a more active part in the ophthalmology of the future

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[1] Sorsby A The Causes of Blindness in England and Wales Medical Research Council memorandum no 24 H M Stationery Office 1950

[2] Sorsby A The Causes of Blindness in England 1948–1950 a report to the Ministry of Health H M Stationery Office 1953

[3] Sorsby A Blindness in England 1951–1954 a report to the Ministry of Health London H M Stationery Office 1956

[4] Sorsby A Blind Certification 1955 in the Report of the Ministry of Health 1955 part II p 218 H M Stationery Office 1956 Sorsby A Blind Certification 1956 in the Report of the Ministry of Health 1956, part I p 215 H M Stationery Office 1957

[5] Ministry of Health Treatment of Cataract and Glaucoma R.H.B. 53 115

[6] Ministry of Health memorandum on the prevention and alleviation of blindness

[7] Davenport R C *Practitioner*, 1957 178 562. Law, F W *Canad med Ass J* 1958, 78, 1

Special Articles

DISRUPTION OF MARRIAGE *

SOME POSSIBILITIES OF PREVENTION

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At the Maudsley Hospital the front page of every patient's notes records whether he or she is single, married, widowed, divorced, separated, or extramaritally cohabiting From this information I have compared the incidence of broken marriages in the three major diagnostic assortments comprised in Section V of the International List of Diseases and Causes of Deaths—namely, psychoses, psychoneurotic disorders, and disorders of character, behaviour, and intelligence The findings, which at first may seem surprising, are shown in the tables Table I sets out the three assortments, adding a fourth or miscellaneous assortment to accommodate patients whose diagnosis placed them outside the others Table II shows a breakdown of the same number of patients into seventeen diagnostic groups that are included in the three major assortments

TABLE I—NO OF BROKEN MARRIAGES (DIVORCES, SEPARATIONS, AND EXTRAMARITAL COHABITATIONS) AMONG 7996 EVER-MARRIED INPATIENT AND OUTPATIENT DISCHARGES IN FOUR MAJOR ASSORTMENTS

(Years 1952–54, Bethlem-Maudsley Hospital, London)

Diagnostic assortment	*Males*			*Females*			*Total*		
	E M	D S C	%	E M	D S C	%	E M	D S C.	%
Psychoses	983	74	7 5	1638	122	7 4	2621	196	7 5
Psychoneuroses	1473	146	9 9	2290	235	10 3	3763	381	10 1
Disorders of character, &c	542	109	20 1	228	64	28 1	770	173	22 5
Miscellaneous	390	38	9 7	452	36	8 0	842	74	8 8
Total	3388	367	10 8	4608	457	9 9	7996	824	10 3

E M, ever married, D S C, divorced, separated, or cohabiting

Among some 8000 patients who have been married (single patients are excluded from the figures) there were 824 broken marriages—an average of a little over 10% But the distributions among the first three assortments vary notably The lowest incidence of broken marriages (7 5%) is in the psychoses In our series of over 2600 ever-married psychotics, patients with schizophrenia and manic-depressive illnesses constitute over two-thirds The next highest incidence of broken marriages (10 1%) is found in the psychoneurotic disorders To our series of over 3700 ever-married psychoneurotic patients, those with anxiety (in its many forms) and reactive depression contributed over two-thirds But much the highest incidence of broken marriages (22 5%) is found in the assortment comprising disorders of character, personality, and intelligence Among these, in our series, people in whom psychopathic and immature personalities had been diagnosed comprised 57%, but a substantial additional contingent was contributed by men with sexual deviations, and addiction to alcohol or drugs

In this third assortment, women did relatively worse than men (table I) The marriages of over 28% of the women broke up, compared with a rate of just over 20% among men, and within this assortment the marriages of men with sexual deviations fared better than might have been expected (table II) There were 89 such men, among whom the marriages of a little over 12% had broken This figure compares favourably with that of over 20% for all the men in the assortment Among patients with sexual deviations, exhibitionists and homosexuals figure prominently It can be surprising how often such men, apart from their abnormalities, make good husbands and have loyal wives

Homosexual activities among women are not in British law a criminal offence For this and other reasons fewer homosexual women than men seek treatment from doctors and hospitals The same can be said about exhibitionism Though the cosmetic industry, the strip-tease act, and everyday experience testify to the presence among women of impulses which could broadly be called exhibitionistic, these activities scarcely ever bring women into conflict with the Law In thirty years' experience, I have dealt with only 1 female exhibitionist who sought medical treatment

Before leaving this topic, I want to make two points clear

First, these figures are not to be taken as in any way representative of *the* collective experience of Britain's mental hospitals My hospital takes into its wards patients who are deemed to be remediable, though many are acutely ill The 7996 ever-married psychiatric patients on whom the two tables are based were mostly referred to the hospital by doctors practising in the southern half of London, these patients are, as far as we know, a fair sample of the inhabitants of South London who become ill enough to be referred by their doctors to a psychiatric hospital for either diagnosis or treatment

TABLE II—NO OF BROKEN MARRIAGES (DIVORCES, SEPARATIONS, AND EXTRAMARITAL COHABITATIONS) AMONG 7996 EVER-MARRIED INPATIENT AND OUTPATIENT DISCHARGES IN SEVENTEEN DIAGNOSTIC GROUPS

(Years 1952–54, Bethlem-Maudsley Hospital, London)

Diagnostic group	*Males*			*Females*		
	No ever married	*Divorced, separated, and extra-maritally cohabiting*		No ever married	*Divorced, separated, and extra-maritally cohabiting*	
		No	*% of ever married*		No	*% of ever married*
Schizophrenic disorders	182	21	12	334	42	13
Manic-depressive reactions	466	30	*6*	781	49	6
Paranoia and paranoid states	52	*5*	*10*	*55*	12	22
Senile psychoses, &c	90	*1*	*1*	*120*	4	3
Organic disorders of the nervous system	(42	3	7)	73	6	8
Other psychoses	151	14	9	275	9	3
Anxiety	483	41	8	605	42	7
Hysteria	108	16	15	247	36	15
Obsessive - compulsive reaction	86	4	5	103	10	10
Neurotic depressive reaction	488	66	14	994	124	13
Other psychoneuroses	308	19	6	341	23	7
Pathological and immature personalities	*278*	*60*	*22*	*164*	*47*	*29*
Sexual deviations	89	11	12	(1	1	100)
Non sexual delinquency or crime	(38	*6*	16)	(17	3	18)
Addiction to alcohol and drugs	137	*32*	*23*	*(46*	13	28)
Miscellaneous	*379*	36	10	*439*	*34*	8
Other groups with small nos of patients	*(11*	2	*18)*	*(13*	2	*15)*
Total	3398	367	11	4605	457	10

Figures relating to totals of less than 50 are in parentheses
Percentages to nearest whole numbers

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* From a paper given at the first conference of the International Planned Parenthood Federation of the region for Europe, Near East, and Africa, held in West Berlin, October, 1957

My second point is that the figures must not be taken as representative of broken marriages in general. Many marriages founder and break without the patients consulting either marriage-guidance services or doctors, and without their being referred to hospitals. When, for example, a married person falls in love with someone else and the marriage is dissolved, doctors and hospitals are unlikely to be involved. My figures are representative of a small segment only of the totality of broken marriages. They may, nevertheless, provide a basis for cautious generalisation.

The main point which emerges is that, among ever-married patients referred to hospital for a wide variety of psychological infirmities, marriages have proved most unstable among the assortment which comprises psychopathic and immature personalities. Why should this be? A possible answer is that an early or recurrent psychosis is commonly felt by the patient's spouse to be outside his control. It is treated as an affliction descending from without. The same may, to a lesser extent, be said of psychoneuroses, of which, as above remarked, over two-thirds were cases of anxiety or depression. Again the illness is commonly felt to be external to the patient, who commonly fights against it. But when a psychopathic or immature personality is diagnosed the position is different. The infirmity here is felt to be not a visitation from without but a factor of his essential personality. It is less a matter of *what the patient suffers from* than of what he *is*.

Psychopathy is less easy to define than either psychosis or neurosis. All I need say is that two types of psychopath are commonly recognised—the inadequate and the aggressive. Psychopaths are well described, in the report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency, as people

> "whose daily behaviour shows a want of social responsibility and of consideration for others, of prudence and foresight and of ability to act in their own best interests. Their persistent anti-social mode of conduct may include inefficiency and lack of interest in any form of occupation, pathological lying, swindling and slandering, alcoholism and drug addiction, sexual offences, and violent actions with little motivation and an entire absence of self-restraint, which may go so far as homicide."

A diagnosis of psychopathic personality is made more often in men than in women.

The immature personality may have features in common with the aggressive, but typically retains the dependency, the egocentricity, or the silliness of childhood. I am myself in the habit of making either a primary or a supplementary diagnosis of immature personality as often in women as in men.

These general considerations of hospital experience may make it understandable why the marriages of people with psychopathic and immature personalities readily founder. I now turn to my own personal experience of those whose marriages, at the time I first saw them, had not actually broken. The marriages were under strain, and it was sometimes in the hope of preventing a rupture that the patient was referred to hospital.

I have asked myself what features of personality most often impair the happiness and stability of marriages. My answer (which as yet I should find difficult to support with figures) is first immaturity, then meanness (for example, over money), and then jealousy.

Immaturity takes two main forms. The first is characterised by excessive dependency, social timidity, and a sense of personal inferiority or inadequacy. These are accompanied by lack of confidence and an insatiable need for reassurance. The possession in common of these misgivings establishes a bond of sympathy between young people which can lead to marriage, but before long frictions develop, because each is making vain demands for reassurance and moral support from the other. A sense of disillusionment generates irritability and irrational feelings of grievance. Things are often brought to a head when either one partner or the other is attracted by someone of more assertive and self-reliant character.

The second kind of immaturity, perhaps commoner among women than men, has as its central feature an egocentricity which blinds the subject to the claims of others. Minor frustration or disappointment is followed by explosions and tantrums, often called hysterical, which are adult equivalents of the temper tantrums of childhood. Marriages thus strained may endure if the spouse is indulgent or pliable, but commonly the worm turns, and either the woman deserts the man, whom she regards as contemptible, or he deserts her regarding her as insufferable. Sometimes the marriage is sustained in a spirit of cold warfare.

I have found that *meanness* in a man will antagonise and estrange a woman more than will acts of violence. I have been astonished at the physical ill-treatment which some women will put up with from periodically intemperate husbands, provided that they later feel and express regret. The woman treats the outburst as somehow out of character and forgives it. Very different is her reaction to intractable meanness or jealousy. These are felt to be despicable traits, forming an integral part of the man's nature, which he makes no effort to combat. Affection and respect—the emotional mainstays of most marriages of people over 50—are slowly undermined and are replaced by hatred and contempt. Among patients more often than among those whose marital troubles do not bring them to doctors, marital jealousy is coloured by a paranoid suspicion. The jealous partner will ransack the pockets and diaries and steam open the letters of the suspected person in search of incriminating evidence. If the marriages of such persons do not break down, they are precariously sustained in an atmosphere of hostility which is one of the nearest approximations to hell-on-earth attainable in modern life.

These and certain non-clinical considerations have led me to the tentative view, which again I could scarcely substantiate with figures, that between 65% and 75% of men and women could, from the standpoint of a matrimonial agency, make good "general-purpose" husbands or wives. By this I mean that they would make good husbands or wives no matter whom they married, provided that the spouse also fell within the wide range of a good general-purpose husband or wife, that another 35–25% require a rather special kind of spouse to make a success of marriage, and that from about 1–3% are next to impossible as marriage partners no matter whom they marry. In suggesting these ratios, I have in mind that between 1% and 2% of people in most countries are sufficiently oligophrenic to be seriously handicapped, and that a large proportion of the deteriorated schizophrenics who spend their lives in mental hospitals are unmarried. I also have in mind the "psychopathic fringe."

Possible Preventive Measures

How far are the factors conducive to the disorganisation of family life preventable? Perhaps they could be reduced to vanishing point by an enhanced knowledge and practice of eugenics and by improved educational programmes. These advances, however, are not yet in sight, and we should not be unreasonably hopeful. Nevertheless something can be done today.

Along eugenic lines much good could be done by the discovery and use of a perfect contraceptive, which could reduce the number of unplanned pregnancies and of unwanted children. I will confine myself to raising one point. I believe that, since the world depression began in 1929, the movements of birth-rates in Western countries have proved that, in an industrially organised, urbanised, and sexually sophisticated country, fluctuations in the standard of living are sensitively reflected by movements of birth-rates In this respect developed countries differ from underdeveloped countries When, during the world depression, unemployment was widespread and living standards fell, the birth-rates of many industrialised countries touched the lowest levels yet on record indeed, fears were widely expressed of an impending depopulation of the West, if not of the whole world (Whether the birth-rates were reduced by contraception or abortion is here immaterial) But the tide turned in a way that few could have expected Insecticides and antibiotics, by causing a fall in death-rates which was almost unimaginable in the middle 1930s, have resuscitated the Malthusian dilemma in a new 20th-century form Since 1945, furthermore, there has been a remarkable wave of prosperity in the West which has kept birth-rates higher than most demographers thought probable ten years ago If we have another depression, it is likely that birth-rates will slump as they did before Many families in what I have called sexually sophisticated countries will then plan down their families to one or two children as they did thirty years ago But the very-small-family system is not wholly beneficial to the child, who can suffer as much from being spoiled as from being neglected The effects of spoiling, moreover, can reverberate through later generations no less than can the effects of neglect and cruelty

Turning from genetic to educative measures, I believe that there exists within our reach a simple, practicable, and economical measure for improving family life—namely, seminars for primigravidæ The argument is this

There is no moment when the average woman is more receptive to guidance as to how to rear her children than when she is pregnant with her first child, and there is no moment when that guidance can be more effectively applied in the prevention of maladjustments and discords, seeing that the beneficiary is not yet born The soil is at its readiest, and the moment for sowing the seed is the best The lessons learned, moreover, stand the mother in good stead when she has more children

I believe that certain elementary principles of pædiatric importance can be effectively inculcated in the course of such seminars The leader of the seminar puts them forward for discussion, and invites each of the participants to comment on them in the light of her own experiences of childhood The women taking part in the seminar have in common the impending crisis of first maternity, so that inhibitions and shyness quickly disappear Indeed, an excellent basis is laid for enduring friendships within the group, the members of which sometimes continue to meet after their deliveries They take an interest in each other's children, who may become playmates

If services for maternity and child welfare exist, it is easy to form a group of from 8 to 12 primigravidæ who expect delivery within about a month of each other The seminars can be held in any convenient premises All that is needed is a room that is pleasantly furnished and a canteen which can provide something to eat and drink—an important requisite in all seminars The premises of a maternity or child-welfare centre might be appropriate, or those of a pædiatric unit, a child-guidance unit, or an obstetric unit More important than the location of the meeting-place is the personality of the person conducting the seminar A married woman of professional status who has herself had children is well placed It is advantageous for her to be a doctor, but in no way indispensable The cost of arranging and holding such seminars is negligible

What principles should be instilled into such a group? Each of us has his own ideas My personal experience has led me to favour the five which follow, of which the first two are scarcely controversial

1 When you are with the baby, be gentle and serene Avoid showing fear, anxiety, or irritability, even if you have these feelings Make the baby feel as safe as you can, and do not be afraid of showing affection or of letting its father show affection

2 Never, if you can help it, leave the child for long in solitude (except at night) during its first three years, and try not to be separated from it for more than a few days If separation is unavoidable, leave it in the care of someone it knows and with whom it feels safe

3 Encourage the child at each stage of its growth to be as self-reliant as possible Give it credit for as much trustworthiness, sense, and initiative as you can Praise and reward it when it shows these qualities, and give it opportunities of displaying them

4 Make for the child as few non-restrictive rules as possible in the light of its age Explain these rules as they are made and also what punishment will be incurred if they are broken If your rules are knowingly broken, punish the child as you said you would do But use all forms of punishment sparingly Steer a middle course between strictness and laxity, also between spoiling and neglect

5 Discuss with your husband the rules you make and the form of discipline you will use as the child grows When these are agreed between you, *back each other up* Children can be clever in exploiting the more indulgent parent, often to the annoyance of the other

These five precepts are simple and can form a basis for discussion at the seminar Many additions will be suggested, and many views advanced, especially on the value of sex education and on the use and abuse of discipline It is rather surprising how some women find these topics difficult to discuss with their husbands these may suggest that husbands be invited to join the seminar This arrangement can be successful Many women will describe their own troubles in childhood The seminar further offers an excellent opportunity to discuss other important matters, such as safety precautions in the home and the physical problems of child care Most important from the standpoint of this conference, it provides the best possible occasion to give instruction on the spacing of children The leader could ask how long the participants in the seminar want to wait before they have another baby and what birth-control methods they think are best Eugenic problems, if they exist, can be discussed

Some women, obviously, will refuse to attend such a seminar, and among them will be women who come from what we call " problem families " These are notoriously difficult to reach and to influence Some women will come but will be too stupid or too immature to benefit Seminars for *primigravid* women, as here suggested, may have been tried in certain countries If so, I do not know of them and I hope that I shall be told

But I am far from supposing that seminars for primigravidæ are a panacea or cure-all I merely claim that they could help many women and do much good for posterity The families of the future would stand to benefit The number of women involved would, at first, be small, but as the seminars (and their leaders) gained in reputation and popularity, the numbers would increase At the end of a vigorously executed ten-year plan, they might be attended by as many as two-thirds of the primigravid women living in the non-rural districts of a country like Britain.

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Public Health

ECHO TYPE-9 MENINGITIS IN EAST SCOTLAND

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IT is now recognised that the clinical syndrome of aseptic meningitis ("non-paralytic poliomyelitis") has often been caused by both poliomyelitis viruses and the group-B Coxsackie viruses Recently an association has also been shown with two of the fourteen serological types of Echo (enteric cytopathogenic human orphan) virus so far identified Cases of aseptic meningitis attributed to Echo virus type-6 were reported in the United States (Karzon et al. 1956, Davis and Melnick 1956), and outbreaks were recorded of a similar illness in Europe (Svedmyr et al 1956, Johnsson et al 1957) A similar illness caused by Echo virus type-9 has been reported in Europe (Tyrrell and Snell 1956, Boissard et al 1957, Quersin-Thiry et al 1957, and Nihoul et al 1957), and in the United States (Sabin 1957)

We here describe the clinical and laboratory aspects of an outbreak of aseptic meningitis caused by Echo virus type-9 in East Scotland from July to November, 1956

Epidemiology

32 patients were admitted to King's Cross Hospital, Dundee, with aseptic meningitis between July and November, 1956 Reports from general practitioners in the area indicated that many more patients were being dealt with at home Of those admitted to hospital, 23 lived within the Dundee City boundary (population 178,946), 5 patients were admitted from Coupar Angus (population 2205) and 1 from the neighbouring village of Newtyle (population <1000) *Towards the end of the* outbreak 3 patients were admitted from the Perthshire village of Bankfoot (population < 1000)

The homes of the Dundee patients were visited and in 9 families there was clear evidence of illness of a similar though usually milder nature, in a further 5 instances there was a similar illness in a contact outside the family circle 4 of the 5 patients from Coupar Angus had contact infection, and from Bankfoot the 3 patients were a mother, daughter, and close family friend In all, there were 4 instances where 2 members of family were admitted to hospital The interval between dates of sickening in these lay between four and six days, and it is suggested that this is a probable incubation period

The age- and sex-distribution is shown in table I The series is small, but the attack-rates for males and females appeared about the same Three-quarters of the patients were between the ages of 5 and 20 years

TABLE I—AGE- AND SEX-DISTRIBUTION

Sex	Age (yr)								
	0-2	2-4	5-9	10-14	15-19	20-24	25-29	30–	All ages
Male	2	4	4	3	4	0	0	0	17
Female	0	0	7	3	3	1	0	1	15
Total	2	4	11	6	7	1	0	1	32

Clinical Features

The main clinical features were

		No of cases		No of cases
Pyrexia		30	Eye pain	6
Headache		29	Abdominal pain	3
Vomiting		28	Drowsiness	6
Neck stiffness—slight	9	27	Irritability	2
—marked	18		Giddiness	3
Kernig's sign—slight	10	17	Nystagmus	1
—marked	7		Rash	3
Muscle pain		9		

The onset was usually sudden. The average time between onset of symptoms and admission to hospital was four days (range one to ten days) A combination of pyrexia, headache, and vomiting, with signs of meningeal irritation, was the most common presenting syndrome 9 patients had muscle pain which was always mild. Pain on moving the eyes was a very definite feature in a few patients in the older age-groups, there was no photophobia A rash was present in only 3 cases—morbilliform in 1 and scarlatiniform in 2 Practically all patients were pyrexial on admission to hospital, temperature ranging between 100 and 102 F The average duration of pyrexia from the onset of illness appeared to be between seven and eight days An interesting feature was a tendency for the temperature to rise abruptly immediately before its final return to normal

Most patients were ill for a few days but recovered quickly and completely No complications, sequelæ, or relapses were observed

Laboratory Findings

Cerebrospinal Fluid

Lumbar puncture was carried out on admission, and subsequently punctures were performed at about weekly intervals until the fluid was approaching normality

Initially the cerebrospinal fluid was invariably under increased pressure, but usually the increase was slight and

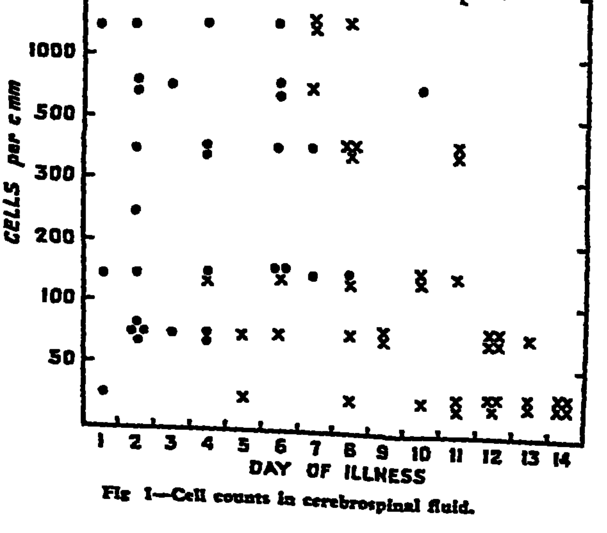

Fig 1—Cell counts in cerebrospinal fluid.

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* Sir Maurice Bloch Fellow in Virology

certainly less than the average in pyogenic and tuberculous meningitis The colour varied between clear and distinctly turbid Many of the fluids were sufficiently turbid to have been confused with the appearances in bacterial meningitis

The cell-counts varied greatly (fig 1), and counts approaching 1500 per c mm were not uncommon even up to the sixth and eighth day of illness In some cases cell-counts, initially low, tended to rise towards the end of the first week and sometimes this was associated with a worsening of the symptoms Cerebrospinal fluid was usually normal or approaching normal by the fourteenth day

Differential cell-counts were done on all fluids and the results related to day of illness are set out in fig 2 During the first four days of illness there was an excess of polymorphs in 8 of 22 fluids examined After the fourth day lymphocytes almost invariably predominated There appeared to be no correlation between the cell-count and the nature of the cell, since an excess of polymorphs or lymphocytes was observed in both low and high counts An observation of interest, if not of practical value, was the presence of rather unusual lymphocytes often in large numbers These cells were large, stained poorly with methylene blue, and were rather "basket-cell-like" in appearance

The protein content did not exceed 160 mg per 100 ml, and in most cases it was less than 100 mg There was no tendency for protein content to increase later in the illness, and if any cell-protein dissociation existed it was in the comparatively low protein contents often associated with high cell-counts Sugar contents were within the normal range

Erythrocyte-sedimentation Rate

The E S R (Westergren) was noted in 19 patients Results ranged between 1 and 32 mm in the first hour

White Count

In 28 patients examined, the count was less than 10,000 per c mm in 18, and in the remaining 10 it ranged between 10,000 and 15,000 per c mm Differential counts were either normal or showed an increase in polymorphs No abnormal cells were found

Virus Investigation

Materials and Methods

A stool and a sample of serum were collected from 24 patients on admission to hospital—i e, at various intervals after the onset of illness A second serum specimen was obtained about ten days after the first Separated serum samples were stored at −20°C

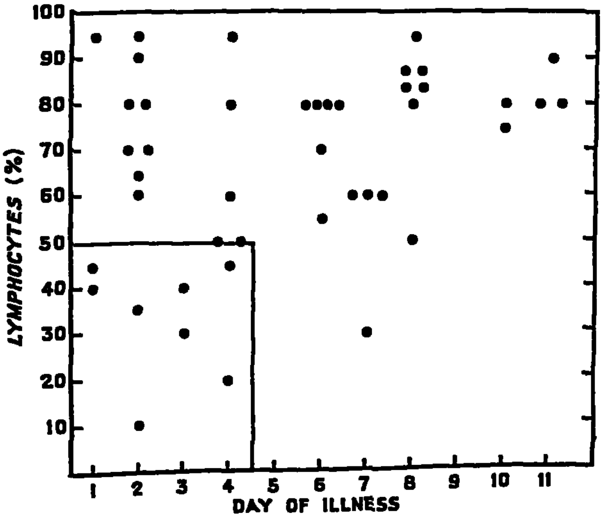

Fig 2—Percentage of lymphocytes in C.S F cells

TABLE II—RESULTS OF VIRUS ISOLATION AND SERUM-VIRUS NEUTRALISATION TESTS ON ACUTE- AND CONVALESCENT-PHASE SERA TESTED WITH ECHO VIRUS TYPES 6 AND 9

Case	Age (yr)	Day of disease acute/ convalescent	Echo-6 antibody titre acute/ convalescent	Echo-9 antibody titre acute/ convalescent	Monkey-kidney tissue-culture of stool
1	3	5/15	*/<8	4/16	Negative
2	7	6/15	*/<8	<2/16	Negative
3	8	6/17	*/<8	<16/128	Echo 9
4	4	12/20	*/<8	<16/64	Echo 9
5	5	5/17	*/<8	<16/32	Negative
6	1	6/18	*/<8	<16/64	Negative
7	2	4/13	*/<8	8/16	Negative
8	10	7/19	*/<8	16/64	Negative
9	7	4/13	*/<8	<16/128	Negative
10	6	9/18	*/<8	<16/128	Negative
11	13	7/19	*/<8	<16/64	Negative
12	6	4/16	*/<8	16/32	Negative
13	3	4/16	*/<8	4/16	Negative
14	5	6/17	*/<8	<16/64	Negative
15	4	6/17	32/32	<16/128	Negative
16	17	9/20	*/<8	16/128	Negative
17	11	5/23	*/<8	8/8	Negative
18	34	2/21	*/<8	16/64	Echo 9
19	18	7/18	*/<8	<16/32	Negative
20	15	10/21	*/<8	16/>128	Negative
21	8	9/21	*/<8	<2/16	Echo 9
22	6	11/23	*/<8	4/16	Negative
23	2	11/26	*/<8	<16/32	Negative
24	0 3	9/27	*/<8	4/4	Echo 9

* Acute serum not tested

Each stool was homogenised in phosphate-buffered saline to make a 10% suspension This was centrifuged at 3000 r p m for thirty minutes and to the clear supernate were added penicillin and streptomycin to a concentration of 100 units and 0 1 mg per ml respectively The fluid was then stored at −40°C

Virus isolations were attempted both in HeLa cells and in trypsinised monkey-kidney cultures prepared according to the method of Bodian (1956) The cells were grown and maintained in Hank's solution with 0 5% lactalbumin hydrolysate and 2% inactivated calf-serum added 0 1 ml of the stool extract material was inoculated into each of 3 tubes of HeLa and monkey-kidney cells, and the tubes, which were incubated at 37°C, were examined daily for cytopathogenic changes Three serial passages were made before a specimen was considered negative in either tissue When cytopathogenic changes were observed, 0 1 ml of tissue-culture fluid was mixed with an equal volume of 1/8 dilution of antiserum, prepared in rabbits, to Echo virus types 6 and 9 The serum/virus mixtures were inoculated into monkey kidney-cell cultures, which were observed for neutralisation of cytopathogenic effect by homologous antiserum

Antibody contents were determined in monkey kidney-cell cultures, with an Echo type-9 virus (719) isolated from 1 patient For purposes of comparison a prototype strain of Echo 9 (Hill) and of Echo 6 (D'Amori) were also used Appropriate dilutions of serum, previously inactivated at 56°C for thirty minutes, were mixed with equal quantities of virus containing 40-50 tissue culture infective doses ($T\,C\,D_{50}$) The serum/virus mixtures were incubated at room temperature for an hour and were then inoculated into duplicate cultures of monkey-kidney cells Tests were read when the virus controls showed complete degeneration, usually at the fourth day Absence of cytopathogenic effect was accepted as evidence of neutralisation The reciprocal of the highest initial dilution of serum producing neutralisation is recorded as the end-point of the titrations

Results

Virus isolations—Cytopathogenic agents were isolated from 5 stool specimens in monkey-kidney cells, whereas none was recovered in HeLa cells All the agents were neutralised by antiserum prepared against Echo virus type-9 and none by Echo-6 antiserum Antiserum prepared against each of the 5 agents in rabbits exhibited reciprocal neutralisation with the homologous virus and the other 4 agents Each antiserum neutralised the prototype Echo-9 (Hill) strain Each virus was inoculated by the intraperitoneal route into suckling mice but no paralysis was observed

Serological results—The results of neutralisation-tests with Echo virus types 6 and 9 on acute-phase and convalescent-phase serum from the 24 patients studied are correlated in table II with the results of virus isolation

A similar antibody titre was observed in each serum tested with the locally isolated strain of Echo 9 and with the prototype virus A fourfold or greater rise in antibody titre to Echo 9 was observed in 20 instances, in 2 a twofold rise was observed and no significant antibody was found in the remaining 2 cases From 4 patients who showed a fourfold rise in homologous-antibody titre, Echo virus type-9 was isolated, but the fifth isolation was from a patient in whom no increase in an initially very low level of antibody was found by the twenty-seventh day of illness 1 patient, whose stool yielded no virus and who produced a diagnostic rise in antibody to Echo virus 9, also had a neutralising-antibody titre of 32 to Echo virus 6 in both acute and convalescent serum specimens, suggesting residual antibody after previous infection with Echo virus 6

Comment

In the clinical diagnosis of aseptic meningitis due to Echo virus type-9 our findings suggest that 3 characteristics are of importance

(1) There is often a familial association between cases, or evidence from the case-history of contact with the disease

(2) The initial severity of the illness is in contrast with the subsequently benign course in all our cases

(3) The various abnormalities in the cerebrospinal fluid even in some cases with an initial predominantly polymorph response, return fairly rapidly to normal

Although the number of viruses isolated was small they all appeared to be antigenically homogeneous The rising antibody titres to Echo virus type-9 in 22 of 24 patients, together with the absence of poliovirus from the stools, provides further proof of the similarity of the infecting agent in each member of the group of patients

Summary

32 persons with aseptic meningitis were admitted to hospital in East Scotland between July and November, 1956 5 viruses belonging to Echo virus type-9 were isolated from the stools of 24 patients Rising titres of antibody to Echo virus type-9 were observed in 22 of the 24 patients examined

We are grateful to Dr Mary Proudfoot, assistant medical officer of health, Dundee, for her help in investigating illness among contacts of patients, to Dr A D Macrae, Virus Reference Laboratory, Colindale, for supplies of seed virus, and to Mr H G Carson, F.I.M.L.T., and Mr J Kerr for technical assistance

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New Arrangements for B C.G Vaccination

The Ministry of Health has issued a revised version of its memorandum[1] on B C.G vaccination. Besides the Danish liquid vaccine used hitherto, the British freeze-dried vaccine will now be introduced, and for the nine months beginning April 1, local authorities may use either type, the position will then be reviewed The liquid vaccine will continue to be supplied as at present through the Public Health Laboratory Service, but the freeze-dried vaccine will be supplied direct by Glaxo Laboratories Diluent will be supplied to local authorities Orders should be placed, as before, through the Ministry of Health, Savile Row, London, W 1 (in Scotland, through the Infusion Fluids Laboratory, 112, Ingram Street, Glasgow, C 1) Vaccine is still available only to hospital and local-health authorities, eligible hospital workers include not only nurses and medical students but anyone at special risk from patients or fomites

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[1] 322 B C.G , see *Lancet*, 1953 ii 1040

Plastics in Food Packaging

When the incidence of food-poisoning is high, the attraction of ready-packed food increases Many plastic materials suggest themselves for packaging, for they can not only be clean but also be seen to be clean, and their poor chemical reactivity makes toxicity unlikely But, though no ill effects have been reported, the plastics industry was concerned lest some material used in processing the plastics might be toxic, and a committee appointed by the industry has suggested a basis for a voluntary standard of performance of plastics[1], maintenance of this standard would exclude a plastic for use with food if it presented any toxic hazard

Medicine and the Law

Duty to Provide Medical Care

THE duty of parents to provide adequate medical attention for children has been emphasised in a warning given by Mr Justice Paull to a couple charged with the manslaughter of their newborn baby[2]

The couple were Jehovah's Witnesses and had refused a blood-transfusion to the baby—apparently on religious grounds The case ended suddenly after the family doctor had said in evidence that he had not warned the parents that failure to give a transfusion would cause the child's death He remembered telling the father that the child should go into hospital for a transfusion, but he could not recall speaking of death

The judge then stopped the case, but told the parents "If after all that you have learned in this court anything like this happens again, the position may be quite different. Just remember that."

There can be little doubt that the judge's warning was fully justified, having regard to the existing law It has for many years been a statutory offence[3] to cause unnecessary suffering to a child by wilful neglect, and the decided cases show that if such neglect results in death the parent or guardian may be guilty of manslaughter The decided cases also show that it is wilful neglect to deny proper medical attention even on grounds of religious objection

In the Queen *v* Morby (1881) the parents were members of a sect known as the Peculiar People and had refused medical treatment for their child The child subsequently died and the parents were charged with manslaughter The parents were acquitted on the ground that the medical evidence did not show that the child's life would necessarily have been prolonged by proper treatment, the doctor said that its life would possibly have been prolonged but he could not say that it would probably have been prolonged

In the Queen *v* Senior (1899)—another case of parents belonging to the Peculiar People—the medical evidence was that proper treatment would have prolonged and would probably have saved the child's life In those circumstances the parents were convicted of manslaughter

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[1] British Plastics Federation report of the 'toxicity' subcommittee of the main technical committee 1958 Pp 20 5s Obtainable from the Federation 47, Piccadilly, London W 1

[2] *Times* March 1, 1958

[3] The current legislation on this subject is the Children and Young Persons Act, 1933

In England Now

A Running Commentary by Peripatetic Correspondents

THE high spot of our last clinical meeting was the Brains Trust—five patients on the platform with a doctor in the chair and an unleavened medical audience The patients were all experienced victims of hypotensive medical therapy (grateful victims, let it be said, for three had presented with retinal hæmorrhage and the other two with cardiac failure) They were soberly authoritative on the merits and demerits of the various drugs, and each had his own way of regulating their side-effects One panellist, a business executive, had become an expert on constipation (senna pods and molasses for him, and a rule that he did not take his morning hypotensive dose until after evacuation) Another, technical director of a large organisation, had sublimated his skills to the taking of his own blood-pressure (he thought his readings could bear comparison with those of the average nurse) A schoolmaster was coping successfully with the twin snags of treatment and the hypertensile effect of prolonged dealings with the young The other members, from being bedridden, had returned to the harassing task of running an hotel and to a job as an industrial foreman

They agreed that it took about eighteen months to adjust to treatment and to learn to live with the disease They laid stress on the problem, to hitherto energetic men, of episodes of depression and of the frustrating languor experienced at times when the blood-pressure had become too low To begin with they had all found a dry mouth troublesome, but this had lessened with time, and they were not favourably impressed by drugs to counteract side-effects They rattled off preparations and dosages with an easy familiarity which emphasised the *pharmacological shortcomings of at least one* member of the audience

Another member, in thanking the panellists, expressed wonder and not a little envy at the chairman's good fortune in acquiring them He had not realised that such intelligent patients existed

* * *

The old grey Social Worker leant forward "He's a good boy, you know," he pleaded "of course I know there's a lot against him, but he thinks a lot of his old Mum and I'd like to carry on and see if there isn't something more I can do for them " He had come half across London to talk about the lad before I wrote the psychiatric report There was indeed a lot against him a string of convictions as long as your arm, child-guidance failure, probation failure, approved-school failure, and now the shadow of borstal was lengthening across his path I knew (though he'd never admit it) that the old man had far too many cases to follow up, and most of them from hard-core problem families whose hides were as leather against the patient permeations of the social services Yet he was proposing to give up more of his rare evenings by the fireside for another thankless (and one feared useless) attempt to salvage this boy There must be a reason for his persistence , he was *involved*, that was it He had allowed his parental instincts to escape control , he had lost objectivity and his reality-testing had gone for a Burton Why, he might even lend the lad money !

It all called to mind the attitude of two symbolic friends of mine One was a young American surgeon of deep Christian convictions who told me with tears in his eyes "When my patients are sick, believe me I suffer every pang with them," and the results of his major surgery in the ghastly climate of the full monsoon were impressive testimony to the value of his prayers My other friend couldn't face this approach , he had fled to the impersonal comforts of the test-tube and microscope "You must know your cases only as numbers and consider each problem in vacuo as an academic one otherwise you die young "

As my emotional state moves me up and down between these two extremes, *I ponder on what I should really feel* about my patients—are they friends, acquaintances, or merely a source of income ? Is the professional relationship an all-excluding one or can I join my patient in the Saloon Bar after psychotherapy, or get him to help me paint the garage doors ? Should I ring up my pals when he's out of a job or send him down to the D R O ? If he's difficult about appointments or rude, do I give him hell and forget him, or try to meet him more than half way ? If one of my depressed *spinsters* gives me as a parting gift a small embroidered (O T) traycloth, do I politely hand it back and mutter about hospital rules ? Or what if she gives me a crate of whisky ?

I suppose, like the old man, I love my patients really, or most of them , perhaps I should get someone to analyse my counter-transference But my love is as nothing compared to his—bless him The report was sent, the court was lenient, he's got his case, and good luck to him I'm afraid he'll need it

* * *

I blame furnaces When I was young I'd come 'ome an' take off me vest an' stand it up on t' floor—stiff wi' sweat

Now then, Doctor doesn't need to know thee pedigree!

Thee pipe down, lass *I'm* tellin' doctor what 'e 'as to know to make a guess at me condition An' I suffered then from t' same symbols as I suffer from now When I pass me wind

Why bring that up ? Doctor can't better thee manners

Me manners ? What's it to do wi' me manners ? When I feel as summat lies dead in me stummick an' embrocation 'as set in—is that me manners ?

Nay lad, but I'll tell thee what it is an' I'll tell doctor what it is—it's beer bottles and barrels of it lyin' flat an' bleak in thee belly, an' it'll save Doctor time if tha told 'im so

Careful, lass!

Where was thee Friday night ? An' Saturday an' Sunday too ? Soakin' it up at t' Oak till it were runnin' out of thee lugs an' breakin' into gas, an' thee trumpetin' through t' night an' waken up in t' mornin' like a shovel-load of cinders in a pot of porridge!

Thou 't in 'igh glee this day, lass Has t' ever thought of joinin' Missions ? She gets like this, doctor 'Er sister Maggie goes round pubs wi' War Cries

Only place to get at chaps like thee

Well, it's 'er only 'ope of gettin' clear of that weak, simperin' tee-totlin' drip of a man of 'ers

* * *

My student days were spent commuting from the middle suburbs to Gower Street By leaving home at 8 14 A M I could just make the 9 A M lecture For Thursdays we had the surgeon's firm promise that he would never start before 9 10 A M This allowed time for an extra slice of toast A readership poll of my travelling companions of those days showed

50%	*Daily Telegraph*
20%	*Express*
20%	*Mail*
0 2%	*Lancet*

If I was very late I would travel with those who are now known as "Top People", or even with *Financial Times* readers Oh, thought I, for the days ahead when as a G P I shall be on the job, with *no travelling*, reading the journals in a fireside peace, away from strap-hanging

These reminiscences were prompted by the clock reading of 10,000 miles which appeared this week on my six-month-old car Even allowing for my wife's shopping, and some fast driving over the straighter roads, this works out at about 1½ hours daily at the wheel A car radio, of course, is one way of making this time more productive, but it can be frustrating, for you tend to arrive at a patient's door just before the climax of a play and emerge in time for the cast list The end result is that you spend more time than ever in the car Perhaps a portable tape playback is a better answer ? We may then look forward to a major metamorphosis of *The Lancet*[1]—its imago form as a spool of tape

* * *

Prof Raymond Dart, of Johannesburg, who has just been awarded the Viking medal by the Wenner-Gren Foundation of New York for his work on human origins, is the author of a paper entitled the *Makapansgat Australopithecine Osteodontokeratic Culture*

Professor Dart is emphatic
That Australopithecine "man"
Was osteodontokeratic,
And that is how Man began!

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[1] *Lancet*, Jan 4, 1958, p 35

Letters to the Editor

BUDGERIGARS AND POLIOMYELITIS

SIR,—Dr Sommerville and his colleagues (March 8, p 512) reported an association between a fatal case of bulbar poliomyelitis and a budgerigar which was excreting type-1 poliovirus The only other reference we know to the circumstantial association of a sick parakeet and poliomyelitis appears in a paper by Fox and Chamberlain[1] In this instance there were four fatal cases of poliomyelitis in one household, but no virus was recovered from the bird

Last week's report has naturally caused anxiety to people owning pet budgerigars, and we feel that a preliminary communication about our studies on the susceptibility of these birds to human polioviruses may be of some interest

A Belfast strain of type-1 poliovirus isolated from the fæces of a paralysed child in 1957 was used for budgerigar inoculation experiments Monkey-kidney tissue-culture (M K T C) passage virus was first titrated in M K T C and then used for the intracerebral inoculation of rhesus monkeys and for the inoculation of budgerigars The paralysing dose$_{50}$ for monkeys was equivalent to $10^{2\cdot8}$ tissue-culture doses$_{50}$ (T C D $_{50}$) of virus, three monkeys being used for each log dilution of virus Three budgerigars were inoculated intracerebrally with $10^{4\cdot5}$ T C D $_{50}$ of virus, and four budgerigars were inoculated orally with $10^{5\cdot3}$ T C D $_{50}$ of virus Three more budgerigars were kept as cage contacts of orally inoculated birds One orally inoculated bird died suddenly on the 5th day this death was considered to be non-specific, as no virus could be recovered from the brain or intestine and contents The other birds remained healthy for 4 weeks Fresh fæcal specimens were collected from all birds for 19 days after inoculation and tested for the presence of poliovirus , None of the birds excreted detectable amounts of virus during this period Serum taken on the 26th day from each bird was tested in M K T C at a 1 in 10 dilution for neutralising antibody against each of the three types of human poliovirus Approximately 100 T C D $_{50}$ of virus was used for these tests No antibody to any of the three poliovirus types was found in the serum of any bird

We consider that our failure to infect budgerigars with a virulent type-1 poliovirus gives hope that the natural infection of these birds may prove to be a rare event

G W A DICK
D S DANE

Department of Microbiology,
Queen's University, Belfast

SIR,—The preliminary communication by Dr Sommerville and his colleagues was most interesting The numerous instances of recurrent cases of poliomyelitis at long intervals in relatively rural areas can be explained only by long-term carriers, but I am convinced that these are more probably human than bird or animal

I wonder whether, in this instance, the carrier state of the rest of the human household is known ? It is only an assumption that the original illness of the budgerigar was caused by poliomyelitis virus An alternative assumption is that some other infecting organism was concerned, the bird subsequently being infected with poliomyelitis virus by a human and acting as a mechanical excreter of virus fed to it from this human source I cannot help wishing that the bird had not been destroyed on Oct. 7, it would have been interesting to see how long the carrier state continued

Mawnan near Falmouth,
Cornwall

E R. HARGREAVES

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[1] Fox M J , Chamberlain J *J Amer med Ass* 1953, 131, 1090

THE MISUSE OF THE TOURNIQUET

SIR,—In the right circumstances a tourniquet is a useful, helpful, even indispensable aid to operating Its use can transform a difficult intricate dissection into a procedure of great simplicity, but it is nevertheless repugnant to the physiologically minded surgeon

It has become customary to use a tourniquet in almost all limb operations, and particularly in the treatment of fractures and the repair of nerve injuries Such a routine is harmful and a backward step in the advance of surgery I hear of tourniquets being left in place, it is said without harm, for two hours or more, even three hours have been mentioned to me This is running two unjustifiable risks the long interruption of the circulation may cause injury to nerves and muscles, the metabolism of the tissues may be so damaged (though the tissues are capable of eventual recovery) that, for a time, the power of immune response is in abeyance and infection follows I am convinced that this is an important factor in the far too common onset of infection after complicated limb dissections Enormous œdema occurs when the tourniquet is removed, and lasts for a number of days During this time the lymph stagnates in the distended tissue spaces The conditions are ideal for the growth of those bacteria which inevitably fall into every surgical wound however stringent the aseptic precautions taken are

It will be said that with a tourniquet applied the operation is not only much easier but much safer and quicker Easier and quicker it may be, but it is not safer for the patient I began my active surgical work in the Arbuthnot Lane era No surgeon at this time ever thought of using a tourniquet when plating a fracture, even the most complicated In the 1914–18 war thousands of nerve sutures were performed without its use I was trained to remove cartilages from the knee without a tourniquet Then for a period I operated with one The postoperative swelling, pain, and increased time needed for recovery were so much greater that I reverted to operating without a tourniquet—but, of course, without the legs dangling over the edge of the table, the customary position, which causes congestion

Tourniquets are not used in the abdomen, in the neck, or within the head In many other places their use is impossible The brachial plexus, for example, must be displayed without one Why, in the case of the limbs, is there this forgetfulness of the vital processes which go on within living cells and their necessary preservation if quick and sound repair is to take place ?

Let me add that in some circumstances a tourniquet is almost indispensable—namely, in such operations as the removal of the palmar fascia for Dupuytren's contracture, to protect the digital nerves, and for the repair of cut digital nerves themselves In any case the very longest time a tourniquet, even a distended windbag, should be left in place is one hour, and ideally that is one hour too long

Basingstoke

CHARLES A PANNETT

TREATMENT OF UNDULANT FEVER

SIR,—I have read with great interest Dr Torres Gost's article (Jan 25) I regret that I cannot share his enthusiasm or his firm conviction that novobiocin (' Cathomycin ') is the ideal antibiotic in the treatment of brucellosis

In 1955 I had the opportunity of using this antibiotic through the courtesy of Prof W Spink, who was then on a visit to Malta Subsequently I received a generous supply from its makers The original intention was to treat 50 cases, but the experiment had to be stopped at 22. With a dosage of 1 5 g daily the results were not so constant or dramatic as those with tetracycline. When 2 g was used the same results were obtained—that is, rapid defervescence and improvement in three to four days—but in 7 cases, exactly on the seventh day, there was a severe urticarial rash with rise in temperature and sometimes headache and vomiting I am afraid that my patients were not of such a Spartan cast as those of Dr Torres Gost, and treatment had to be stopped

In the 15 patients who completed a fifteen-day treatment, there were 5 relapses (bacteriological) within four months, which is roughly our figure when tetracycline is used In the 7 patients who did not complete the course there were 4 relapses within two months

I was brought up in an old school, and my aim has always been to treat patients *tuto, cito, jucunde* I will not go so far as to say that novobiocin is dangerous, but the rash and the fever do not add to the *jucunditas* of the patient. It has no advantages over the tetracyclines, and in my opinion its usefulness lies in another sphere—in the treatment of staphylococcal pneumonia and of bronchiectasis, where the results are really marvellous

After the generosity of the makers of novobiocin, I feel somewhat reluctant to write this letter I can justify my action, to myself, only by another Latin tag—*amicus Cæsar sed magis amica veritas*

St Luke's Hospital,
Valletta, Malta
J E Debono

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

Sir,—Does Dr Schuurmans (March 8) consider that "it is highly probable that the increased frequency of toxæmia of pregnancy and pre-eclampsia in patients with beri-beri" (in whom he states the adrenals are hyperplastic) "and pellagra" (in whom he infers that the adrenals are atrophic) "must be ascribed to the adrenals too"? Is it possible that both excess and deficiency of adrenal secretion equally provoke toxæmia?

London, W 1
John Sophian

ILEOSTOMY CHEMISTRY

Sir,—You refer to our work on electrolyte losses from an ileostomy stoma in your annotation of March 8 Dr Abbott and his colleagues, in a letter last year,[1] questioned the high levels of sodium output we obtained in the immediate postoperative period (approximately 300 mEq per litre) As you have observed, it is difficult to understand how such a high concentration can occur, we think that we now have an explanation

We checked the methods we had employed[2] against duplicate estimations undertaken in another laboratory The results always tallied Since no error could be found in technique we considered once more sodium intake, more particularly since estimations undertaken in more recent cases have only occasionally revealed the high output we observed at the beginning of our investigations some four years
he
methods of administering sodium and the quantitie
not substantially altered Inquiry revealed, how
the source of supply of salt tablets was changed by
pensary about two years ago because of complaints
appeared undigested in the normal stools of other pa
whom they had been administered Our patients receive
tional salt by mouth as soon as the ileostomy begins to fun
in two forms—by "enteric-coated" capsules prepared i
hospital dispensary and by supplied by a phar
ceutical company which a form of "enteric coating We have observed neither in undigested form at any time in the 24-hour collections from which aliquots were taken for our estimations It is quite possible, however, that such tablets passed with the ileostomy excreta in semi-digested form, then dissolved in the cans during the 24-hour collection period or perhaps when the contents were mixed prior to sampling, thus increasing the sodium concentration

This seems to us to be the probable explanation, though we have not as yet been able to reproduce our earlier findings by administration of the offending tablets Nor can we explain why, if our hypothesis is correct, the tablets have failed to dissolve properly in the intestines immediately following the institution of an ileostomy but have dissolved subsequently, and, furthermore, have done so following subsequent operations when they were administered, as before, and the sodium concentration has never been elevated above 150 mEq per litre

Queen Elizabeth Hospital,
Birmingham
N Crawford
B N Brooke

THE LIFE FOR ME

Sir,—One of the virtues of Dr Richard Cobbleigh's Widdicombe letters is their briskness My attempt to emulate it has led him (March 8) to misunderstand my use of his own term "those Clinics" I used it about maternity and child-welfare centres in the sense he did about twelve months ago, when reflecting in an earlier letter on his not very extensive experience of them Of course, any good G P can do this work—a good many in London in fact help us by doing it But that in no way disproves the functional value of the M & C W centre as such As a medium for health education, as a forum for a mild gossip, as a convenient place to get food for the baby, as a means of giving a mother some feeling of security about her offspring, and as a convenient building for various prophylactic injections, it has uses most of which escaped Dr R Cobbleigh Nor is it more likely to be a source of infection than a doctor's surgery

But this is old stuff London, like other local authorities, is now feeling its way (I think the phrase is reasonably accurate) towards the contribution it can make to preventive mental health Any doctor or health visitor, knowing of a family with a problem in which there is a psychological or psychiatric aspect, can seek guidance at a case conference in the centre presided over by a psychiatrist The field worker presents the case The psychiatrist can (*a*) ask for more facts which the field worker proceeds to get, (*b*) indicate lines of approach to the family which may solve or *ameliorate the problem*, or (*c*) recommend reference to a specialist

This is slow work Though we have such conferences
available in eac ur nine health divisions we are
finding that th orkers need about two years'
regular attenda ese meetings before they are
reasonably com to act on their own and to
know when the beyond them But the system
shows signs of self and lot of field
workers graduat al, w spread the
ining to other ychia *are helping*
(paid for by hos s) we owe
t debt
preventive clinic is
and much one has
d a meth method
ly invol of years
can as much

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[1] Abbott W L, Levey,
[2] and 1957 i, 864
cet, 1957, ii, 149

with and on the parents as with the child The importance of the preventive work we are essaying (quite apart from man-power considerations) is indicated by the fact that about 80% of the children referred to L C C child-guidance clinics, at whatever age they come, are so referred because of difficulties which originated before the child was five years old

Public Health Department,
London, S E 1

J A SCOTT
Medical Officer of Health for the County of London

EXPOSURE ON MOUNTAINS

SIR,—Exposure in mountaineers usually involves physical exhaustion as well as exposure to cold On high Scottish hills it is often unpredictably cold, and the damp atmosphere further intensifies cold effects Fierce winds may also contribute to conditions more conducive to hypothermia and exhaustion than those encountered at higher altitudes elsewhere in the world.

Severe physical effort leads to anoxia, and the combination of anoxia and extreme cold may induce ventricular fibrillation This fatal event may ensue very quickly when the body is exhausted as well as cold, the idea that under such circumstances death is slow is erroneous, and so is the commonly accepted advice to keep moving at all costs Those benighted on high hills in winter must strictly conserve their energy and find shelter, or at least some kind of wind-break, till conditions improve One has safely lain out at heights over 3000 feet on hard winter nights, wearing only ordinary climbing clothing, while waiting for dawn to get casualties down It is safe if one is not exhausted

Often in mountain tragedies women have survived when men under similar strain have succumbed I feel certain that women have the tougher constitution for this sort of ordeal, but it is hard for a male-ruled world to accept this, and women survivors have more than once been accused of causing the death of a male companion A woman's power of endurance is illustrated by an accident in which four men died but a girl of comparable physique, with normal subcutaneous fat and similarly clothed, survived

With four very fit men, one of whom was her husband, she had to struggle against a gale, said to reach 100 m p h , for 3-4 miles down a gently sloping snow-covered valley in Inverness-shire One of the men began to tire, the girl and her husband supported him, following in the track of the other two who went ahead it was nearly impossible to look up into the gale Then they changed places, the other two supporting the weak one A few minutes later the girl looked back at the three behind, and the weak one was not there, the others said, "He was out so we left him " Later she wrote "I couldn't have had much feeling left, because I merely said Oh' and continued walking as if it were an everyday occurrence to leave one's friends lying in the snow in a deserted glen "

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Belford Hospital,
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D G DUFF

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—I read with interest, and growing surprise, Dr Ryle's letter (March 1) about Dr Clyne's article of Feb 1 In the last sentence he administers the final blow by calling Dr Clyne's approach "unscientific" Now Dr Ryle is himself a family doctor and a very good one, and he should know that the emotional forces which operate within the doctor–patient relationship are as real, and as potent for good or ill, as any physical agent Of course the disease must be described and investigated, that is part of the doctor's job, and it must be done thoroughly The other part is the understanding and management of a personal relationship, and the "charges" of feeling that exist there These, too, need to be described and investigated—objectively and in detail, as Dr Clyne has done They cannot be measured, as yet, but they can be studied—this is the first phase of any scientific inquiry I think there is no doubt at all that more study of, and more teaching of the student about, what goes on between doctor and patient will in the end yield great benefits for everyone concerned

London, W 1

DESMOND O'NEILL

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SIR,—In his letter of Feb 8, Dr Robertshaw described a patient who, three days after receiving an intraglossal injection of suxamethonium, had pain and swelling of the tongue and cervical adenitis, which subsided with penicillin therapy This picture suggests bacterial infection The pain and swelling following chemical irritants injected intramuscularly is noticed within twenty-four hours, and usually begins to disappear in three days (e g , chlorpromazine)

I have had no such complaint in five years of this practice, and I have personally followed up ten patients who, since Feb 8, have received 100 mg suxamethonium intraglossally None of these patients made any spontaneous complaint none had pain or swelling of the tongue The only positive finding was aching and stiffness in the neck muscles for two days in two patients, attributable to the intraglossal suxamethonium, this was mild, and the incidence is similar to Hegarty's figure[1] for intravenous suxamethonium

Chislehurst Kent

JOHN BULLOUGH

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[1] Hegarty, P *Brit J Anaesth* 1956 28 209

experiment had to be stopped at 22 With a dosage of 1 5 g daily the results were not so constant or dramatic as those with tetracycline When 2 g was used the same results were obtained—that is, rapid defervescence and improvement in three to four days—but in 7 cases, exactly on the seventh day, there was a severe urticarial rash with rise in temperature and sometimes headache and vomiting I am afraid that my patients were not of such a Spartan cast as those of Dr Torres Gost, and treatment had to be stopped

In the 15 patients who completed a fifteen-day treatment, there were 5 relapses (bacteriological) within four months, which is roughly our figure when tetracycline is used In the 7 patients who did not complete the course there were 4 relapses within two months

I was brought up in an old school, and my aim has always been to treat patients *tuto, cito, jucunde* I will not go so far as to say that novobiocin is dangerous, but the rash and the fever do not add to the *jucunditas* of the patient It has no advantages over the tetracyclines, and in my opinion its usefulness lies in another sphere—in the treatment of staphylococcal pneumonia and of bronchiectasis, where the results are really marvellous

After the generosity of the makers of novobiocin, I feel somewhat reluctant to write this letter I can justify my action, to myself, only by another Latin tag—*amicus Cæsar sed magis amica veritas*

St Luke's Hospital,
Valletta, Malta

J E Debono

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

Sir,—Does Dr Schuurmans (March 8) consider that "it is highly probable that the increased frequency of toxæmia of pregnancy and pre-eclampsia in patients with beri-beri" (in whom he states the adrenals are hyperplastic) "and pellagra" (in whom he infers that the adrenals are atrophic) "must be ascribed to the adrenals too"? Is it possible that both excess and deficiency of adrenal secretion equally provoke toxæmia?

London, W 1

John Sophian

ILEOSTOMY CHEMISTRY

Sir,—You refer to our work on electrolyte losses from an ileostomy stoma in your annotation of March 8 Dr Abbott and his colleagues, in a letter last year,[1] questioned the high levels of sodium output we obtained in the immediate postoperative period (approximately 300 mEq per litre) As you have observed, it is difficult to understand how such a high concentration can occur, we think that we now have an explanation

We checked the methods we had employed[2] against duplicate estimations undertaken in another laboratory The results always tallied Since no error could be found in technique we considered once more sodium intake, more particularly since estimations undertaken in more recent cases have only occasionally revealed the high output we observed at the beginning of our investigations some four years ago The methods of administering sodium and the quantities given had not substantially altered Inquiry revealed, however, that the source of supply of salt tablets was changed by the dispensary about two years ago because of complaints that they appeared undigested in the normal stools of other patients to whom they had been administered Our patients receive additional salt by mouth as soon as the ileostomy begins to function, in two forms—by "enteric-coated" capsules prepared in the hospital dispensary and by tablets supplied by a pharmaceutical company which also have some form of "enteric" coating We have observed neither in undigested form at any time in the 24-hour collections from which aliquots were taken for our estimations It is quite possible, however, that such tablets passed with the ileostomy excreta in semi-digested form, then dissolved in the cans during the 24-hour collection period or perhaps when the contents were mixed prior to sampling, thus increasing the sodium concentration

This seems to us to be the probable explanation, though we have not as yet been able to reproduce our earlier findings by administration of the offending tablets Nor can we explain why, if our hypothesis is correct, the tablets have failed to dissolve properly in the intestines immediately following the institution of an ileostomy but have dissolved subsequently, and, furthermore, have done so following subsequent operations when they were administered, as before, and the sodium concentration has never been elevated above 150 mEq per litre

Queen Elizabeth Hospital,
Birmingham

N Crawford
B N Brooke

THE LIFE FOR ME

Sir,—One of the virtues of Dr Richard Cobbleigh's Widdicombe letters is their briskness My attempt to emulate it has led him (March 8) to misunderstand my use of his own term "those Clinics" I used it about maternity and child-welfare centres in the sense he did about twelve months ago, when reflecting in an earlier letter on his not very extensive experience of them Of course, any good G P can do this work—a good many in London in fact help us by doing it But that in no way disproves the functional value of the M & C W centre as such As a medium for health education, as a forum for a mild gossip, as a convenient place to get food for the baby, as a means of giving a mother some feeling of security about her offspring, and as a convenient building for various prophylactic injections, it has uses most of which escaped Dr R Cobbleigh Nor is it more likely to be a source of infection than a doctor's surgery

But this is old stuff London, like other local authorities, is now feeling its way (I think the phrase is reasonably accurate) towards the contribution it can make to preventive mental health Any doctor or health visitor, knowing of a family with a problem in which there is a psychological or psychiatric aspect, can seek guidance at a case conference in the centre presided over by a psychiatrist The field worker presents the case The psychiatrist can (*a*) ask for more facts which the field worker proceeds to get, (*b*) indicate lines of approach to the family which may solve or ameliorate the problem, or (*c*) recommend reference to a specialist

This is slow work Though we have such conferences available in each of our nine health divisions we are finding that the field workers need about two years' regular attendance at these meetings before they are reasonably competent both to act on their own and to know when the problem is beyond them But the system shows signs of justifying itself and as one lot of field workers graduates, so to speak, we hope to spread the training to others To the psychiatrists who are helping us (paid for by the regional hospital boards) we owe a great debt

The preventive value of a child-guidance clinic is another and much more complex matter No-one has yet evolved a method of evaluating it, any such method would clearly involve observation over a period of years But no clinic can succeed unless it works at least as much with and on the parents as with the child The importance of the preventive work we are essaying (quite apart from man-power considerations) is indicated by the fact that about 80% of the children referred to L C C child-guidance clinics, at whatever age they come, are so referred because of difficulties which originated before the child was five years old

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[1] Abbott W L Levey S, Krieger, H *Lancet* 1957, ii, 119

[2] *ibid* 1957 i, 864

J A SCOTT
Medical Officer of Health for the County of London

Public Health Department,
London S E 1

EXPOSURE ON MOUNTAINS

SIR,—Exposure in mountaineers usually involves physical exhaustion as well as exposure to cold On high Scottish hills it is often unpredictably cold, and the damp atmosphere further intensifies cold effects Fierce winds may also contribute to conditions more conducive to hypothermia and exhaustion than those encountered at higher altitudes elsewhere in the world

Severe physical effort leads to anoxia, and the combination of anoxia and extreme cold may induce ventricular fibrillation This fatal event may ensue very quickly when the body is exhausted as well as cold, the idea that under such circumstances death is slow is erroneous, and so is the commonly accepted advice to keep moving at all costs Those benighted on high hills in winter must strictly conserve their energy and find shelter, or at least some kind of wind-break, till conditions improve One has safely lain out at heights over 3000 feet on hard winter nights, wearing only ordinary climbing clothing, while waiting for dawn to get casualties down It is safe if one is not exhausted

Often in mountain tragedies women have survived when men under similar strain have succumbed I feel certain that women have the tougher constitution for this sort of ordeal, but it is hard for a male-ruled world to accept this, and women survivors have more than once been accused of causing the death of a male companion A woman's power of endurance is illustrated by an accident in which four men died but a girl of comparable physique, with normal subcutaneous fat and similarly clothed, survived

With four very fit men, one of whom was her husband, she had to struggle against a gale, said to reach 100 m p h , for 3-4 miles down a gently sloping snow-covered valley in Inverness-shire One of the men began to tire, the girl and her husband supported him, following in the track of the other two who went ahead it was nearly impossible to look up into the gale Then they changed places, the other two supporting the weak one A few minutes later the girl looked back at the three behind, and the weak one was not there, the others said, "He was out so we left him" Later she wrote "I couldn't have had much feeling left, because I merely said 'Oh' and continued walking as if it were an everyday occurrence to leave one's friends lying in the snow in a deserted glen"

Then two of the men began to lag behind "All three of the boys' eyes were glassy looking, bloodshot and unable to focus properly They kept asking me if I was all right and would I make it I never doubted that we would all make it I said it was about a quarter of a mile to the bridge, although it turned out to be nearer a mile" One asked her how many steps there were in a quarter of a mile "It was then I realised the boys were more exhausted than me"

Soon the men could not walk against the wind "I kept lifting up the boys as they fell, and no sooner had I one up than the other would fall I dragged them into a wee gully where the wind was slightly less strong I tried to keep them warm and awake, and I fed them on chocolate and sweets They fell asleep in about ten minutes after getting into the gully It took us about half an hour to cover the last 30 to 40 yards during which the boys began to lose their senses They stopped breathing about twenty minutes after they fell asleep The boys most definitely were not in pain and their death was quick and peaceful I think their senses were numbed and they just fell asleep and died quietly They didn't even seem to feel the cold and I know I didn't in spite of being soaked to the skin and lying in the snow Although they lost their senses of sight and feeling, they definitely could still hear, because, in the gully, I chatted to the boys and my husband smiled when I spoke, although he just looked straight ahead and didn't say anything I did not feel the wind as much as the boys and I have found that before" She struggled to a house and, after a wash and a hot drink, quickly recovered She suffered no ill effects, but the four men died

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Chislehurst Kent

JOHN BULLOUGH

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[1] Hegarty P *Brit J Anæsth* 1955 28, 209

BONE-MARROW DEPRESSION FOLLOWING TREATMENT OF TETANUS WITH PROTRACTED NITROUS-OXIDE ANÆSTHESIA

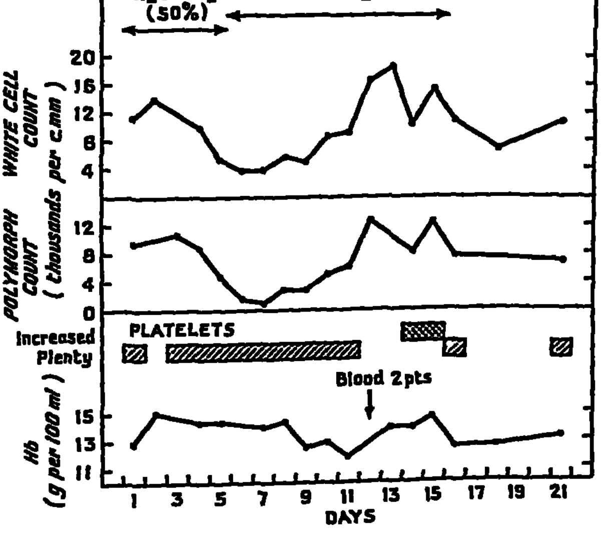
SIR,—In cases of tetanus treated by curarisation and artificial respiration, Lassen and his colleagues[1] presented evidence to suggest that bone-marrow depression was due to commercial nitrous oxide used for prolonged sedation We report a further case which supports this conclusion

A shearer and rabbit-trapper, aged 57, was admitted to the Royal Adelaide Hospital on July 7, 1957 Fourteen days previously he had cut the pulp of the ring finger of his right hand Four hours after he reached hospital and forty hours after he first complained of backache and difficulty in opening his mouth, he had a generalised severe tetanic spasm The terminal segment of the infected finger was amputated, under local anæsthesia, after 300,000 units of antitetanic serum had been administered Next morning, difficulty in coughing and swallowing made tracheotomy necessary

Six hours after tracheotomy, though sedation had been carried to the stage of "periodic" breathing, he still had tetanic spasms in response to stimuli, and it was decided to give tubocurarine and to begin artificial respiration using a respirator with positive and negative pressure phases A mixture of 50% oxygen and 50% nitrous oxide was administered for continuous sedation through the carbon-dioxide absorber unit of an anæsthetic machine

Before curarisation the patient was given penicillin, streptomycin, mepyramine maleate, chlorpromazine, and paraldehyde, and mephenesin and promethazine by intermittent intravenous drip Of these, only penicillin and streptomycin were continued

On admission the hæmoglobin was 15 g per 100 ml, and the leucocyte-count 18,300 per c mm, of which 90% were neutrophils Daily examinations thereafter revealed a progressive fall, and on the fifth day the leucocyte-count was 5200 per c mm, of which 86% were neutrophils At this juncture nitrous oxide was stopped, and the gas mixture was changed to (approximately) air 60% and oxygen 40%, with oral chloral hydrate and paraldehyde as basal sedatives



On the sixth day, the leucocyte-count had fallen to 3500 per c mm with 28% neutrophils, showing an Arneth shift to the right On the seventh day the hæmoglobin was 13 9 g per 100 ml, reticulocytes less than 0 1%, platelets 230,000 per c mm, and leucocytes 3600 per c mm., with polymorphs 27%, lymphocytes 48%, monocytes 10%, eosinophils 4%, and plasma cells 11%

During the succeeding days, the white-cell count rose rapidly to normal levels, which were maintained, but the hæmoglobin fell to 11 3 g per 100 ml on the eleventh day Tubocurarine was stopped on the fifteenth day, and the tracheostomy tube was removed five days later

Leucopenia, anæmia or thrombocytopenia have been previously described in 9 patients with tetanus treated by curarisation and artificial respiration, and all except 1[2] had been given long-continued nitrous-oxide anæsthesia

Lassen[1] first attributed this bone-marrow depression to commercial nitrous oxide, and his suggestion was supported by Wilson et al[3] In our case the leucocyte-count began to fall on the third day, but the depression was greatest on the fifth and sixth days after beginning nitrous oxide, this corresponds with the interval recorded by Lassen, by Wilson et al,[3] and by Last and Nicholas[4]

A number of other drugs have been common to the reported cases, including antitetanic serum, tubocurarine, and penicillin, but we feel that the improvement which followed the cessation of nitrous-oxide administration is strong evidence that this, or a contained impurity, was the toxic agent, particularly since no change was made in the other drugs being given at this time

A high oxygen-tension has been shown to affect hæmatopoiesis,[5] but the bone-marrow apparently has not been depressed despite extensive use of 50% oxygen and 50% nitrogen mixtures in respiratory units for bulbar poliomyelitis, and it seems unlikely that the relatively small change in the proportion of oxygen in the inspired gases in this case could cause and reverse changes of such magnitude

We wish to thank Dr C B Sangster and Dr R A A Pellew, under whose care this patient was admitted to the Royal Adelaide Hospital, and Dr N G Marshall, director of anæsthesia

Royal Adelaide Hospital,
Australia

M J W SANDO
J R LAWRENCE

A NEW PINK DISEASE

SIR,—Since mercury was withdrawn from "teething-powders", pink disease in this region has almost disappeared But a new syndrome has appeared which has claims to usurp the discarded title

CASE 1—A baby boy began to vomit intermittently and stopped gaining weight at 6 months of age He was referred to hospital in his 30th week, when he looked reasonably well, weighing 17 lb There were no abnormal physical signs The mother said his napkins turned bright pink when washed This was specially noticeable with soiled napkins and less so with urine-soaked ones The colour appeared as soon as the napkin was placed in soapy water, but napkins belonging to a baby cousin, put into the same water, remained white The mother denied that the child had had any liquid paraffin emulsion, 'Petrolagar', 'Agarol', or any other medicine at all

CASE 2—A baby girl, aged 8 months, had had sudden recurring attacks of crying, sweating, and drawing up of the knees for 3 weeks The bowels were regular, and there had been no vomiting There were no abnormal physical signs and the baby's weight was 21 lb 10 oz The mother had been in the habit of giving her magnesia two or three times in each week and she was advised to stop this A week later she said that there was no improvement and the baby was still having two or three attacks every day On this occasion she also remarked that the baby's soiled napkins turned bright pink when put into the washtub As in the first case, all aperients and medicines, apart from the magnesia, were denied.

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[1] Lassen, H C A, Henriksen, E, Neukirch, F, Kristensen, H S *Lancet*, 1956, i, 527

[2] Mollaret, P, Bastin R Damoiseau, B, Goulon, M, Pocidalo, J J, Rapin M *Pr méd* 1955, 63 1413

[3] Wilson P Martin F I R, Last P M *Lancet*, 1956, ii, 442.

[4] Last P M, Nicholas J *Med J Aust* 1956, ii 373

[5] Tinsley, J C Jr Moore C V, Dubach R., Minnich V, Grinstein M *J clin Invest* 1949, 28 1544

The solution to both problems came on subsequent occasions in response to a very specific question, " Do you give the baby teething-powders ? " For both mothers this was apparently so normal and usual an administration as not to count as a " medicine " They were advised to stop giving teething-powders and the symptoms in the babies ceased.

In early editions of *The Extra Pharmacopœia*, ' Steedman's Soothing Powders ' were said to have an average weight of gr $2^{1}/_{3}$ and to contain 27% calomel In the most recent edition they are said to weigh gr $2^{1}/_{2}$ and to contain no calomel, but 32 61% of phenolphthalein—that is, more than gr $^{4}/_{5}$ Compared with other purgative preparations containing phenolphthalein this is a substantial dose for an infant of 6 months Emuls paraff. liq et phenolphthal. *B P C* contains less than gr $^{1}/_{2}$ per drachm, a usual dose for a child of this age 'Petrolagar (Red Label)', a proprietary equivalent, has a similar amount, although 'Agarol', another, contains more Tab phenolphthal co *B P C*, and 'Alophen Pill', a proprietary equivalent, contain only gr $^{1}/_{2}$, although they also contain aloin gr $^{1}/_{4}$ No-one would suggest that a single dose of phenolphthalein gr $^{4}/_{5}$ is likely to harm a young infant, but presentation as a " soothing-powder " may well encourage regular, even daily, administration by some mothers, and increasing administration if the child is other than soothed

Unless the administration of " soothing-powders " is specifically asked about, the explanation of the vomiting or colic may remain obscure This syndrome could be even more perplexing if the napkins were washed with soaps or detergents less alkaline than those used in the two cases presented here

Department of Child Health,
University of Durham,
at Newcastle upon Tyne

E G KNOX

EFFECT OF HEAT ON SPASTICITY OF DISSEMINATED SCLEROSIS

SIR,—A phenomenon which, as far as I know, has not been recorded is that spasticity is much increased when patients with disseminated sclerosis are exposed to high temperatures This condition is easily corrected by reducing the blood temperature below normal by a cold shower or bath

Disseminated sclerosis may be caused by a thrombocyte-agglutinating substance in the cerebrospinal fluid Persson[1] suggested that penetration of this agglutinating substance into the small veins of the central nervous system may be responsible for the periventricular thrombus formation and also for thrombosis in the small veins of the central nervous system Increase in plasma-fibrinogen during the active phases of the disease may also contribute to thrombus formation

In view of the increase in prothrombin-times following the exposure of man to wet thermal atmospheres,[2] over 30 cases of disseminated sclerosis, varying from mild to severe, were treated under these conditions combined with anticoagulant therapy The severe cases became so spastic that further treatment was impossible, while in the less severe cases favourable results were obtained

All these patients said that their weakness and spasticity increased in warm weather and that they felt better in the cold It was noted that all mouth temperatures were subnormal

It is interesting to note that disseminated sclerosis is more prevalent in temperate climates than in the tropics, and this raises the question whether this condition is connected with lower metabolism, blood temperature, and thrombus formation

Tunbridge Wells

E F ST JOHN LYBURN

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[1] Persson, I *Arch Neurol Psychiat* 1956 76, 313

[2] Lyburn, E F St J *Lancet* 1957, ii, 745

CORTISONE IN THE TREATMENT OF ACUTE INFECTIONS

SIR,—I am disappointed that none of my colleagues has so far responded to my invitation (Nov 16) to come forward with his experience of cortisone in the acute infections, the more so as some, I know, have been using it. Meantime, as I have been accused of using it in " hit-or-miss " fashion, and as I have had a number of letters from doctors, may I put forward my views in a little more detail ?

Let me concede at once that experiment and experience alike suggest that, should infection be sustained—or introduced—under cover of cortisone, the results may be disastrous inasmuch as the defences may be subdued and signs and symptoms of what is afoot may be minimal until irreparable damage has been done The position, however, is vastly different once the defences have been seriously challenged and aroused Here, in a certain number of cases, the situation is reversed, and the danger arises, not from the sluggishness of the body's reaction, but from its unbridled vigour

In any epidemic, it is reasonable to assume that the infective agent is of uniform virulence and invasiveness Those infected may be divided into (1) the insusceptible or immune who do not react at all, followed in ascending order of susceptibility by those who experience (2) subclinical, (3) mild, (4) moderate, or (5) severe attacks Finally (6) there are hyper-reactives who might be described as allergic to the parasite and who may kill themselves—and frequently do—by the vehemence of their response as expressed in hæmorrhages (into the adrenals and elsewhere), collapse, exudates, effusions, adenopathies, intractable vomiting and diarrhœa, and so on, unless something is done to curb the reaction It is here that cortisone is invaluable, and so frequently saves life. Such fulminating reactions occur most commonly in meningococcal infections (Waterhouse-Friderichsen syndrome) and probably also in certain cases of smallpox and hypertoxic diphtheria, but it appears they may also occur in other conditions—e g., the cases described by Dr Barrowcliff and Dr Prior (Dec 14) and Dr Warrack (Dec 21) where the parasite was presumably the influenza virus

Obviously, when using cortisone so early in the infective process, two questions are of prime importance Firstly, does cortisone inhibit the action of the antibiotics and, secondly, does it hinder the development of immunity ? As regards the first, I can only say that if it does I have not been able to detect it clinically In respect of *immunity, it is only reasonable* to assume that cortisone will retard its development, but I know of no real evidence on the subject. In any event, since the only alternative to its use in these cases is a fatality, the question seems of academic importance

Neither of these considerations apply when invoking cortisone at a later stage in the infective process when, in spite of days or more commonly weeks of therapy, the patient is going steadily downhill and a fatal outcome seems inevitable. Whether in such cases a gradually developing adrenocortical exhaustion is a major factor in this decline and, if so, why one adrenocortical steroid out of approximately a score should apparently prove competent to arrest it are questions I am unable to answer, but the fact is that cortisone has turned the tide in far too many cases to admit of coincidence as a reasonable explanation. Perhaps, however, instead of theorising, I may quote a few representative cases

The value of cortisone in the Waterhouse-Friderichsen syndrome is no longer in dispute There are numerous references to it in the literature and I myself with others have chronicled two cases[1] I will therefore confine myself to its use in other conditions

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[1] Breen G E., Emond R T D, Walley, R V *Lancet*, 1952 i, 1140

The first case was an infection with an unidentified pyogenic organism (possibly a resistant staphylococcus) The second was probably an erythema multiforme, and the last two are examples of glandular fever, presumably virus in origin

CASE 1 —A man of 33, admitted on March 18, 1956 A month previously he had food-poisoning on board ship to New York where he had treatment with some improvement Diarrhœa recurred on return voyage, complicated by melæna shortly after arriving home On admission he was sharply febrile and very ill During subsequent days, severe hæmorrhages from the rectum Found to have ischiorectal abscess with fistula-in-ano, and ? early peritonitis Blood-transfusion on March 20 followed by laparotomy which revealed turbid fluid in the peritoneal cavity Abscess laid open at the same time No pathogens grown from either source After operation high fever persisted with copious oozing from abscess cavity and by March 27, despite treatment including frequent transfusions, the patient was moribund Placed on intravenous glucose drip with cortisone (120 mg in twenty-four hours) and erythromycin Response immediate Within twenty-four hours patient afebrile, mentally clear, sitting up, and taking nourishment by mouth Following further transfusions, colostomy on April 13, closed on June 22 Discharged fit on July 9

CASE 2 —A boy of 16, admitted on Nov 12, 1955, ill since Nov 3 On admission, sharply febrile, profuse desquamation of face and trunk together with (*a*) Stevens-Johnson syndrome (stomatitis, conjunctivitis, and urethritis), (*b*) meningism, (*c*) paraplegia of lower-motor-neurone type, (*d*) arthritis of right hip, and (*e*) acute enteritis Lumbar puncture 12 cells per c mm , fluid otherwise normal Urine normal Condition deteriorated steadily Nov 17, pericardial effusion Nov 18, effusion in both knee-joints, and cortisone (25 mg t d s) begun Immediate response Afebrile within twelve hours By Nov 23 power had returned to legs, and heart-sounds were normal. Discharged fully recovered on Jan 10

CASE 3 —A girl aged 19, admitted April 10, 1957, the twelfth day of a severe attack of glandular fever Fauces and tonsils very œdematous and covered with membrane, gross cervical adenitis (bull neck), and copious bloodstained nasal discharge Severe anæmia (Hb 40%) As she could not swallow and her nose was impassable to a catheter, she had to be maintained intravenously Her condition deteriorated steadily despite several transfusions On April 13 there was much albuminuria with widespread crepitations over both lungs and by April 16 she appeared moribund (racing feeble pulse, peripheral cyanosis, and delirium) Cortisone (125 mg in twenty-four hours) included in drip, again with an immediate response Within twenty-four hours the temperature had fallen and in forty-eight hours the throat and glands had much receded and she was taking food by mouth Subsequent progress uneventful Discharged well on May 15

CASE 4 —A similar case of glandular fever A boy of 8 years, admitted on Oct 10, 1957 There was high fever, gross angina, bull neck, copious nasal discharge, and the patient was stuporous Prednisone (10 mg t d s) was begun at once On the following day I failed to recognise the patient His temperature was normal, the glands were scarcely visible, and the nasal discharge had ceased He was sitting up in bed making a hearty dinner I have included this case because anyone who has seen a florid and actively developing infectious reaction virtually obliterated in twenty-four hours (without elimination of the organism) can hardly fail to question much of our current theory on the genesis and purpose—if any—of such reactions, and indeed of the whole nature of infectious disease in general

I have now used cortisone or its derivatives in some 70 selected patients over the past five years Most were P U O s for which, despite diligent inquiry, no cause could be found, some showed the stigmata of collagen disease But there were many others lung and bowel infections (including infantile gastroenteritis) and infections of the central nervous system (*Hæmophilus influenzæ* meningitis, pneumococcal and meningococcal meningitis, and an extreme rarity, a monkey-B2-virus encephalomyelitis) I have used it with restricted objectives to reduce gross palpebral œdema in herpes ophthalmicus with iritis and corneal ulcer, to control copious secretions in a case of bulbospinal poliomyelitis on intermittent positive-pressure respiration (Intimidated by experimental reports, this is the only case of poliomyelitis in which I have had the courage to use it so far) Very seldom have I been disappointed I was not impressed by the response in a case of (probable) polyarteritis with peripheral neuritis, nor had it any observable effect in a case of hæmorrhagic chickenpox (thrombocytopenic) with severe recurrent epistaxis Only once have I had reason to suspect a harmful side-effect—in a man of 78 admitted pulseless and semicomatose, with widespread bronchopneumonia who died thirty-six hours after admission At necropsy there was fairly free bleeding from a recent peptic ulcer which may or may not have been due to prednisone

The last thing I wish to do is to encourage the indiscriminate use of cortisone or its derivatives But I submit that we have here a weapon of immense power in the treatment of the acute infections which not only saves life but has much to teach us by what it does and, perhaps still more, by what it fails to do It is surely essential that its applications and limitations should be clearly defined as soon as may be At present there is obviously much confusion Thus a recent " authoritative " review states that cortisone is contraindicated in tuberculosis This contrasts strangely with the findings of the Research Committee of the Tuberculosis Society of Scotland [2] which showed that prednisolone-treated cases did better than the controls without it We need more reports of this type based on careful clinical trials rather than on conjecture or misleading animal experiments Once again, therefore, I would appeal to those who have used cortisone in the infections to give us the results of their experience

South Middlesex Hospital,
Isleworth

G E BREEN

SIR,—The possible use of cortisone in influenzal pneumonia has lately been discussed in your columns, and I should like to record the following unhappy experience

An Arab, aged about 40, came to hospital because of fever, cough, rusty sputum, and pain in the chest for two days X-ray examination showed bilateral basal pneumonia Temperature 102° F White-cell count 4800 per c mm Erythrocyte-sedimentation rate 25 mm in 1st hour Generalised rhonchi and coarse râles in the chest

During a secondary epidemic of influenza, a diagnosis could be made with some certainty The antibiotics chosen were streptomycin and isoniazid because it was felt that an underlying tuberculous infection could not be ruled out Penicillin was added after four days because there had been no response to streptomycin, but no clinical benefit followed

It was then decided to give the patient hydrocortisone (50 mg intramuscularly three times a day) His condition thereupon rapidly deteriorated dyspnœa became the most prominent symptom, pulse and temperature soared, and a radiograph showed almost total consolidation of both lungs The patient died twenty-six hours after the first dose of hydrocortisone

It is unreasonable to draw conclusions from one experience, but this case supports the view expressed by Dr Librach (Dec 7)

Qatar
Persian Gulf

R T S LOUTTIT

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[2] Brit med J 1957, ii 1131

MANIPULATION FOR BACKACHE

SIR,—We should like to congratulate Mr Bremner on his article of Jan 4 dealing with manipulation in the management of chronic low backache due to "lumbosacral strain"

We agree that the lesion of lumbosacral strain is a degeneration, most commonly of the L5/S1 disc (we include the L4/L5 disc less commonly), with involvement of the posterior joints by laxity at first, followed by osteoarthritis

Before any form of treatment is contemplated a more exact diagnosis should be attempted Claims for the replacement of a slipped disc are often made when the condition is really due to involvement of other structures forming a spinal segment, or when, in the older patient, the condition is the result of an aggravation of a pre-existing spondylosis, signifying itself in disc degeneration and osteoarthritis

The value of any form of treatment and the prognosis will depend on the type of onset, the phase the condition is in at the time of treatment, the patient's age, the effect of previous treatment, and the type of sciatica (true or pseudo)

Certainly, manipulations without anæsthesia, especially as carried out by Dr Hargrave-Wilson (Jan 11), can help in many cases, but it is our contention, in support of Mr Bremner, that manipulation with anæsthesia also has a place in the treatment of certain cases

Manipulations without anæsthesia should never be carried out forcibly against severe muscle spasms, but if they are performed gently, especially when previous muscle spasm has been reduced by heat, massage, spraying with ethyl chloride, or procaine injection, they often relieve symptoms immediately Muscle spasm, denoting joint irritation, must be coaxed rather than forced No sensible medical practitioner will rely on any one form of treatment in this condition

It must be remembered that the lumbosacral region is one of the prime fixing levels in the body, because it is at the junction of the trunk and the pelvis Remedial exercises and postural training are, therefore, an essential part of treatment

Low back pain may be a symptom in the following groups of patients

(1) Those with postural and occupational strain, causing first, muscle strain, then joint strain This condition can begin at any time but usually shows itself before the age of 25 Manipulation under anæsthesia is often indicated in the younger athletic patient, with a history of injury some months previously, who has pain on movement in one direction only

(2) Those with low back pain, of acute onset, associated with lumbago and sciatica This denotes a joint strain in which one or more of the components of a vertebral segment have become involved, either by injury or in a degenerative process The average age for this type is 25–35 In this group it is of paramount importance to distinguish between a true sciatica and a pseudo-sciatica Patients with lumbago only often get better in three weeks, but manipulation without anæsthesia can often relieve the symptoms in a few days If there is true sciatica no experienced doctor is likely to recommend manipulation under anæsthesia until he has tried every form of conservative treatment and is prepared to operate immediately, especially if the symptoms are aggravated In this type of case disastrous results may follow any type of manipulation, for a piece of sequestrated loose disc may be pushed further backwards through the posterior longitudinal ligament, with pressure on the cauda equina or sciatic roots Untreated patients of this group tend to pass into the next group

(3) Those with chronic lumbosacral strain (without radiographic evidence of spondylosis) signifying disc degeneration and osteoarthritis This is the group which Mr Bremner is considering the average age being 39 in his male patients and 35 in the females The first group may gradually pass into this group, or an acute exacerbation may produce group 2 If the condition is due to a lesion of the apophysial or posterior intervertebral joints, immediate relief may be expected from manipulation without anæsthesia By appreciation of certain physical signs and symptoms, one can diagnose many of these lesions and expect an immediate result If the patient fails to improve after manipulation without anæsthesia, it is well worth trying the effects of a controlled manipulation under anæsthesia before resorting to disc operation or spinal fusion

(4) This includes those patients with chronic lumbosacral strain and radiographic evidence of spondylosis Most are over 50 Manipulation without anæsthesia can play an important part in the relief of symptoms An acute exacerbation, through an unguarded movement, may give rise to lumbago, true sciatica, or pseudo-sciatica

Let us always try to be more specific in our diagnosis Are we dealing with a muscle strain or joint strain with or without disc involvement? Is the disc involvement an internal derangement between the vertebral bodies, or an external prolapse through the posterior longitudinal ligament, or is there an aggravation of a pre-existing spondylosis? Many patients are improved by bed rest, a plaster jacket, various forms of support, manipulation, injections, various types of physiotherapy, elimination of septic foci, or treatment of gout The psychiatric approach and deep X-ray therapy must not be despised Operation in the chosen case may become essential and can give a degree of permanent relief of symptoms obtained by no other method

The conditions of low back pain pass through so many phases, it is only by careful assessment of the signs and symptoms of these that the right treatment can be arrived at

London, W 1

W E TUCKER
R P GOULDEN

TREATMENT OF HEPATOCEREBRAL INTOXICATION

SIR,—The treatment of hepatocerebral intoxication by influencing the urea cycle and related reactions has been very encouraging in our experience of over one year Some of the implications of present knowledge of the urea cycle[1] seem not to be fully appreciated We should like, therefore, to emphasise the following points

Ammonia is converted into urea only in the liver at the steps involving the transformation of ornithine into citrulline

$CO_2 + NH_3 + ATP$ + (catalytic amounts of carbamyl glutamate) + ornithine → citrulline

In a similar reaction, if ornithine is replaced by aspartate and the corresponding enzymes, the active carbamyl intermediate is converted into carbamyl aspartate, which is the first intermediate in the biosynthesis of pyrimidines and, therefore, of nucleic acids The second nitrogen of urea enters as amino nitrogen (aspartate)

Citrulline + aspartate + ATP → arginine → urea + ornithine

Thus, for every turn of the cycle, 1 mole of free ammonia, 1 mole of amino nitrogen, and 1 mole of carbon dioxide are transformed into urea via the catalytic action of ornithine and of carbamyl or other N-acyl glutamate derivatives (acetyl glutamate has been identified as the physiological agent)

The prevention, by arginine, of the toxic effects produced by ammonia administration and those of amino-nitrogen administration cannot be directly compared, since ammonia is converted into aminoacids only by reductive amination of α-ketoglutarate followed by transamination

In normal people the Krebs urea cycle should function with adequate enzymes, intermediates, and substrate concentrations, therefore increasing only one substrate (presumably ornithine from the administered arginine) may not necessarily increase the overall rate of urea formation in the normal liver

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[1] Grisolia, S, Rainey, R B in Amino-acid Symposium Baltimore, 1955

Therefore, ideal therapy based on present knowledge should include (*a*) elimination of the source of ammonia, and (*b*) the administration of arginine and carbamyl glutamate, the latter for acute or chronic hepatic failure as well as for liver regeneration

Since carbamyl glutamate is easier and cheaper to make than acetyl glutamate we have been using this catalytic agent for some nine months (intravenously as 3 g of the potassium salt combined with 10 g of arginine, oral dose 1-2 g daily), with good results Finally, this treatment may be reinforced by binding the excess ammonia via formation of glutamine analogues in vivo as a temporary measure to aid the overloaded urea cycle Attempts are in progress to combine these therapeutic measures

University of Kansas
Medical Center

R BROWN
R MANNING
M DELP
S GRISOLIA

P A.S AND THE PATIENT

SIR,—We should like to comment on the article by Dr Dixon and his colleagues,[1] in which they report that 50% of their outpatients on P A S. therapy have been found, as a result of a single urine test, to have defaulted in taking their P A S

It is generally accepted that P A S prevents resistance to streptomycin and isoniazid, and that its toxicity is low Its importance in combined long-term treatment has, therefore, never been contested so far Being administered by mouth, it is particularly suitable for ambulant therapy and for children Combined isoniazid–P A S has gained further support since it was realised that P A S delays the inactivation of isoniazid by inhibiting its acetylation [2]

To deal with gastrointestinal disturbances during oral treatment with P A S and isoniazid, two definite improvements have been made first, by introducing combined preparations in an attempt to overcome the unreliable P A S ingestion [3], and secondly by evolving P A S preparations based on benzoyl-P A S, like calcium B–P A S Owing to their greater acceptability[4] and more satisfactory gastrointestinal tolerance,[5 6] these preparations make uninterrupted P A S therapy easier

It is surprising, therefore, that Dixon et al report little or no difference in the "default-rate", whether the drugs are given separately or in combined form, and whether P A S or B–P A S is prescribed

Your annotation [3] advises examination of the causes of the failure to take P A S, before the well-proven ambulant chemotherapy with isoniazid and P A S is dropped We wonder whether the results obtained under the chosen experimental conditions justify such a far-reaching conclusion It is hard to tell, because neither the single doses of the P A S preparations nor the time intervals between these doses and the urine analyses are given

Dixon et al recommend the ferric-chloride test for the control of both P A S therapy and B–P A S However, on theoretical considerations alone, the colour reaction due to B–P A S is 50% weaker than that due to the same weight of P A S, because the benzoyl radical constitutes an important fraction of the B–P A S molecule On checking Dixon's modified ferric-chloride test in a small number of volunteers, we found that, after administration of 3 5 g of calcium B–P A S, the colour reaction in the urine excreted in the sixth hour after medication was not always positive After giving 3 0 g of sodium P A S, however, the test was positive and stronger in all cases It may therefore be possible that Dixon's test is not sufficiently sensitive for B–P A S, thus leading to wrong conclusions regarding default of patients taking B–P A S The same applies to the tests involving hypochlorite and Ehrlich's reagent, which were used by Leggat[7] for controlling P A S medication

To make it suitable also for controlling B–P A S treatment, the test cannot be rendered more sensitive under Dixon's experimental conditions by diminishing the dilution of the urine, for basic iron salts precipitate and interfere with the reaction

The sensitivity may, however, be increased by adjusting the pH to 2 5—3, which is optimal for the reaction and within which range less iron phosphate is precipitated With the aid of a glycine-HCl buffer of pH 2 5, urine can be diluted 1 30, in which dilution neither alkalinity nor excessive urinary phosphates will interfere with the ferric-chloride reaction Since, however, B–P.A.S is sparingly soluble at this pH, the buffer must contain ethyl alcohol The following buffer is suitable for use in testing for both P.A.S and B–P A.S

Glycine (aminoacetic acid)	1 728 g
Sodium chloride	1 350 g
0 1 *N* Hydrochloric acid	270 ml
Distilled water	*230 ml*
96% ethyl alcohol	500 ml.

Should the pH of the buffer differ from 2 5 by more than 0 5 units, it must be corrected by adding a few ml of either 0 1 *N* hydrochloric acid or sodium hydroxide

To check whether P A S or B–P A S is being taken, 0 1 ml of urine is diluted with 3 ml of glycine buffer, and 1 drop of ferric-chloride solution (3 g of $FeCl_3$, 6 H O in *100 ml of distilled water*) is added In the presence of P A S derivatives, a red-violet colour results If, in urine containing large amounts of phosphates (e g morning urine), clouding is observed due to precipitation of iron phosphate, the reaction is produced by adding one more drop of *ferric-chloride* solution

Unlike Dixon et al we have found that their ferric-chloride test on subjects who had been given 1 g of aspirin was positive in the urine excreted in the sixth and in the twelfth hour after medication

The intention of these comments is, first, to suggest that, in certain circumstances, Dixon's modified ferric chloride test may be fallacious as regards the detection of B–P A S defaulters and to suggest an improvement of his method, and, secondly, we should be happy if this would help to re-establish, at least in part, the honour of the patients who were suspected of making misleading statements

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Berne, Switzerland.

H LAUENER
T FRIEDRICH

SYLLABUS FOR EXAMINATIONS IN PSYCHOLOGY

SIR,—I am a senior clinical psychologist in a mental hospital who, as part of her duties, tries to give some help to doctors who are preparing to take their D P M, part I, in which psychology is one of the subjects

Psychology is not an easy subject for people trained in medicine, because it uses different concepts and a different vocabulary Furthermore, its boundaries are extremely wide, and the English Conjoint Board does not publish a syllabus to guide candidates in their studies If they turn to previous papers for guidance they find little help, since within the past two years questions have been set on as widely varying topics as the electroencephalograph, the value of the concept of psychosomatic disorder in general practice, and the theory of the structure of consciousness by Janet Two of these topics come only very generally within the confines of psychology, and the third is of academic interest only, as the relevant work was published in 1890 One would not quarrel with this so much if there were a published syllabus to some item of which the question could legitimately refer

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[1] Dixon, W M, Stradling P, Wootton, I D P *Lancet*, 1957, ii, 871
[2] Favez G, Lauener, H *Schweiz med Wschr* 1956, 86, 1395
[3] *Lancet*, 1957, ii, 881
[4] Gibson, M O J, Nagley, M M *Tuber le*, 1955, 36, 209
[5] Hudson, E H in Heaf, F R G, Symposium of Tuberculosis, p 321 London, 1957
[6] Stahle, I *Acta tuberc scand* 1957, 34, 83
[7] Leggat, P O *Lancet*, 1957, ii, 1283

This problem is particularly acute for doctors who are working on their own in provincial hospitals, and whose contacts with universities and access to big libraries are limited to occasional visits to London.

As the universities publish syllabuses for their D.P.M. psychology examinations, cannot the Conjoint Board do the same?

St. James' Hospital,
Portsmouth

A. M. SILVER

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—I should like to mention a stern test I gave the nylon darn in 1952.[1]

This concerned a man of 82 who came to Nottingham General Hospital with an inflammatory mass in the right upper scrotum, which was found to be due to an appendix abscess in a hernial sac. Having removed the appendix and excised the sac I carried out a single layer darn, using no. 5 monofilamentous nylon. No. 5 nylon was used to close the external oblique. The wound healed with only a mild superficial infection, and when I last heard from the patient a year later there had been neither recurrence nor sinus trouble.

Satisfactory healing under such unfavourable conditions bears out Mr. Moloney's original contention that "nylon tends not to be disturbed by the misfortune of sepsis."

Dublin

VICTOR LANE

Parliament

The Minister's Review

ON March 5, moving the second reading of the National Health Service Contributions Bill, which was carried by 308 votes to 252, Mr. DEREK WALKER-SMITH, the Minister of Health, took the opportunity to discuss some of the general issues of the economics of the service. The cost of the service has risen from £452 million in 1949–50 to £740 million, and he began by pointing out that this increase of £288 million, allowing for changes in the value of money, was an increase in real terms of £80 million.

Another way of measuring the cost of the service was as a percentage of the gross national product, and this percentage, which had been dropping for some years until 1954, had since risen slightly. He himself distrusted this percentage as a ready reckoner of the health and progress of the service. He believed that we should aim to expand the gross national product as much as possible and spend on the health service the highest common factor of what we needed and what we could afford. The ideal situation would be to get a sustained and rapid increase of the national product coupled with a sustained and steady fall in calls on the health service owing to the reduction of illness, yet that ideal situation would lead to a declining percentage. Conversely if the gross national product fell the percentage spent on the service, though the money was actually static, would rise. Yet this would not mean that the health service was doing better but merely that the country was doing worse.

Returning to the present increase of £288 million, he pointed out that since in terms of real money this was only an increase of £80 million, we were left, after making minor adjustments to allow for the increase in the population and in the proportion of old people, with £200 million which was due to inflation. It was not the prodigal habits of the service which were forcing the inflationary pace. The increase reflected the inflationary tendencies in the economy as a whole.

Measured in terms of services rendered as well as in terms of money spent, the contributor, in Mr. Walker-Smith's view, was getting good value. Despite our economic difficulties the money available for capital works on hospitals was increasing. Bed occupancy had risen from 453,000 in 1950 to 478,000 in 1956, and outpatient attendances from 31 million to over 35 million. In 1951 there were 20,500 general practitioners, in 1956 22,500, and the number of patients per doctor had fallen from 2500 to 2272. The number of dental treatments had risen from $9^1/_2$ million in 1953 to 12 million in 1956, and of sight tests from $4^1/_2$ million in 1951 to $5^1/_2$ million in 1956.

The increased productivity and value of the service was not of course inconsistent with the possibility of economies being found without detriment to the patient. Could the inflationary increase, or any substantial part of it, be met by economies in the service, apart from the general arrest of the inflation in the economy as a whole? The pattern of expenditure according to the 1958–59 estimates was: hospital running costs £399 million (about 54% of the total cost), hospital capital cost £23 million (3%), general medical services £72 million (10%), pharmaceutical services £74 million (10%), dental services £51 million (7%), local authority services £65 million (9%). Thus more than half the money went on hospital running costs; these were mainly wages and commodities and the rise in their cost reflected the general inflationary tendency. There remained the possibility of economies in administration, and to that end he had instituted the technique of "organisation and methods" in hospitals in the hospital service. It was started in September, 1954, with an experimental hospital organisation and methods unit recruited from the Treasury and the Ministry. By September last this unit had completed 78 assignments covering a large number of aspects of hospital work at individual hospitals. It had also undertaken, and had nearly completed, 8 comparative studies involving the examination of important common procedures or services at a large number of hospitals. The subjects included under these comparative studies were methods of analysing expenditure, arrangements for compiling and maintaining inventories, methods of stores accounting and arrangements for outpatient departments. The experience of these three years had shown that the application of the various techniques used by organisation and methods investigation in business, industry, and public administration could produce valuable results in the hospital field. The value of this work had been recognised by the Estimates Committee, and he was now considering the best way to establish organisation and methods procedure as a permanent and integral part of the hospital service.

He realised that there was some doubt or even disquiet about the size of the drug bill which, at £74 million, had more than doubled since the start of the service. There were two causes: the general rise in costs, and the introduction of new drugs. But the new drugs had made a great contribution, not only in the social sense, but also to the national economy in mitigating the effects of diseases like tuberculosis, pneumonia, and acute rheumatism. They were keeping the drug bill under scrutiny and trying to confine it to its lowest reasonable cost.

It was clear, he thought, that the main element in the steady, and hitherto apparently uncontrollable, rise in the cost of the health service was a reflection of the general inflationary tendency in the economy. The health service clearly had a prime interest in countering and reversing inflation, because only so could it hope to achieve its own economic stability and salvation, and the principle of unlimited Exchequer liability was clearly inconsistent with a disinflationary policy. It was in the context of these principles that the modest adjustment in the pattern of payment contained in this Bill must derive its justification. In no other country was the scale of service equal to ours. In most countries it was done mainly on the basis of health insurance rather than on the basis of a national scheme, and in few countries did even health insurance cover all. Often, even in enlightened and progressive countries like the Netherlands, France, and Western Germany, the Government contributed nothing to the insurance scheme.

For ten years the efforts to control expenditure on the health service had been rather makeshift and piecemeal. We had been working our way rather as in a tunnel, with our eyes fixed not much further forward than our feet. He believed that we could now see some light at the end of the tunnel and a sounder financial future for the service To many it was a paradox that its improved efficiency, productivity, and output was not reflected in a diminution of disease and consequent diminution of treatment and cost The answer was twofold First, many of the new drugs and treatments were necessarily expensive and the immediate impact was to increase costs Secondly, because of the war and the consequent arrears the first impact of increased productivity had been to reduce waiting-lists and accelerate treatment But something of what could be done in the future had been shown by the dramatic reduction in the calls on the hospital service—for example, in the case of tuberculosis He hoped that this pattern would be repeated in other ways, especially by arranging for community care instead of hospital care for more old people and more of the mentally ill

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[1] Lane, V. J. Irish med. Ass. 1954, 35, 284.

The National Health Service could have a sound financial basis only if we got rid of its inflationary elements, and since these reflected the general position, we could succeed only by ridding the whole economy of its inflationary virus It was not the financial basis of the health service only which depended on this for success Inflation and the social services could not coexist in the long run The social services were strong in themselves, but they could not be stronger than sterling

Medicine and Television

On March 7 Mr Ernest Marples, the Postmaster-General, *made the following statement**

At question time on Feb 26[1] I referred to the B B C's consultation with medical authorities about the programme *Your Life in Their Hands* This seems to have given rise to some misunderstanding I would like to clear up this misunderstanding

I am informed by the B B C that the Corporation had had wide and detailed discussions with medical, surgical, and nursing staffs both on the subject matter of the programmes as well as their method of presentation Before the first broadcast, the B B C held a conference At this conference, representatives of the Royal College of Surgeons and the Royal College of Physicians and members of the College of General Practitioners were present, together with other interested medical men and representatives of the medical Press Nothing occurred as a result of this informal consultation to suggest to the B B C that its programmes would meet with opposition from the bodies concerned or that the Corporation ought not to proceed *with its plans Correspondence* after the first broadcast from members of the medical profession and others confirmed the B B C in this view

I regret that the information I previously passed on to the House implied a more formal degree of consultation between the B B C and the medical bodies mentioned as well as a formal expression of their subsequent appreciation of the programme This appears to have arisen from a misunderstanding between my department and the Corporation

QUESTION TIME

Senior Registrars

Mr Kenneth Robinson asked the Minister of Health when he expected to meet the Joint Consultants Committee to discuss the senior registrar problem —Mr Derek Walker-Smith replied Tuesday, March 25

Mr Robinson Will the Minister, since there has been an effort over a long period to reach an agreed solution in this matter, give an assurance that he will, if necessary, impose his own just solution on the profession and see that no medical or vested interests are allowed to stand in the way of its implementation?—Mr Walker-Smith I would not like to enter into a discussion of this sort on any assumption other than that reason will prevail and that we shall get an appropriate and reasonable solution harmoniously by agreement together

Mr John Cronin asked the Minister on how many occasions representatives of his Department have had meetings with the Joint Consultants Committee during the last two years to discuss the difficulties of senior registrars in the National Health Service —Mr Walker-Smith replied There have been ten meetings at which the general question of hospital medical staffing, including the senior registrar aspect, has been discussed

Mr Cronin asked the Minister why he had made it a condition for relieving the difficulties of senior registrars that the medical profession should agree to the setting up of a number of new special posts, not previously provided for in the National Health Service, in which the duties were similar to those of consultants, whereas the salary and status were substantially inferior to those of consultants —Mr Walker-Smith No such condition has been made

Cost of Prescriptions

Mr Arthur Blenkinsop asked the Minister of Health what was the average cost per prescription issued under the National Health Service as at the latest available date, how this compared with the cost one year and two years previously, and what analysis had been made to establish the cause of any increase —Mr Walker-Smith replied Approximately 6*s* 1*d* in December, 1957, as compared with 5*s* 6½*d* in December, 1956, and 4*s* 7½*d* in December, 1955 Examination of representative samples of prescriptions shows that the main reason for the increase in December, 1956, and subsequently was the prescribing of larger quantities Since December, 1955, the cost has also been affected by the prescribing of certain expensive preparations which had not previously been available

Mr Blenkinsop Does the Minister not recognise that this is a confession that the increased prescription charge has resulted in higher costs to the nation because of the larger quantities his Department encourages doctors to prescribe? Will he not meet the problem sensibly by withdrawing the charge?—Mr Walker-Smith Although there is a higher prescription charge, partly due to the larger quantities but also partly due to the new drugs, the number of *prescriptions in 1957, even* with the influenza epidemic, dropped substantially below the number of prescriptions in the previous year Mr Blenkinsop Does not the Minister agree, in spite of the fact that there is a reduction in the number of prescriptions, that the increased quantities in prescriptions have resulted in a very considerable increased charge to the community, and therefore does he not agree it is time we abolished the charge?—Mr Walker-Smith I do not think that conclusion follows from the position as we have it now There are certain respects in which the prescription of large quantities is justifiable If there is over-prescription on unjustifiable occasions, that is one of the things we shall hope to deal with after having the advantage of the advice of Sir Henry Hinchliffe's Committee and any other advice we may receive

Number of Dentists

It is estimated that by July 5, 1958, about 1500 dentists in general practice, who will have reached age 60 or more, will then be entitled to retire on pension under the National Health Service Superannuation Regulations on completing ten years' service

Private Practices

Mr Blenkinsop asked the Minister of Health on what basis it was assumed that earnings from private practice by general practitioners amount to £2 *million a year and* that this figure has *remained unchanged since* 1948 —Mr Walker-Smith replied The figure of £2 *million* has been used in the calculation of the central pool because Mr Justice Danckwerts adopted it in his award From and including the financial year 1952–53 it has been used on a provisional basis and is subject to retrospective adjustment should it be found by inquiry to have been too high or too low

Organisation and Methods Service

Sir Keith Joseph asked the Minister how many staff were engaged in the Hospital Organisation and Methods Service, what assignments were at present being undertaken by it, and whether he could yet announce how much he proposed to extend this service —Mr Walker-Smith replied 9 8 comparative studies and 12 individual assignments are in hand In addition, 20 assignments at individual hospitals have been accepted but not yet started I am considering how, and in what form, this service can best be extended SIR KEITH JOSEPH Without exaggerating the virtues of this technique, does not the Minister feel that a staff of 9 is grossly inadequate when put to use in such a vast organisation employing almost the third largest manpower force of the whole country, and when he comes to consider what he proposes to do, will he bear in mind that much benefit could be gained by circulating the results of each inquiry, as it is held, to comparable institutions so that all may benefit?—Mr WALKER-SMITH The last part of the question is really more applicable to the comparative studies than to the individual assignments, because of the variety of circumstances to which the individual assignments relate The studies so far put in hand result from the experimental unit which was set up to see whether this Organisation and Methods system would be of value in the hospital service I think it has been clearly shown to be of value, and I am actively considering the best way to make this a permanent feature integrated in the hospital service

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[1] See *Lancet*, March 1, 1958, p 539

Nurses' Overtime

Mr FENNER BROCKWAY asked the Minister if he would authorise payments to nurses for overtime duties—Mr WALKER-SMITH replied This question has so far arisen only in respect of mental and mental-deficiency nurses who are already paid for excess hours worked—Mr BROCKWAY While recognising that and that the conditions for nurses have considerably improved, since they are still much lower than those for industrial workers, may I ask the Minister at least to see that their devotion is not exploited by the refusal of payment when they do overtime?—Mr WALKER-SMITH No claim for payment of this sort has so far been made for the general nurses, and as far as I know none is contemplated

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Obituary

WILLIAM QUARRY WOOD

M.D, Ch.M Edin, F R C S.E, Hon F R.F P S

Mr Quarry Wood, who died on Feb 28, was one of Edinburgh's best-known surgeons and an outstanding exponent of his art In recent years he had become an elder statesman to whom many of his colleagues turned for sound advice and friendly help

Born in 1888 at St. Boswells, he graduated M B from Edinburgh University in 1911 After serving as a house-surgeon in the Royal Infirmary he took the F R C S E in 1914, and later he proceeded to the degrees of M D and CH M, on both occasions winning a gold medal He was a clinical tutor to the Royal Infirmary before he was appointed an assistant surgeon in 1923 He held this post till 1939, when he became surgeon-in-ordinary Besides his surgical appointments he was lecturer in anatomy to the University in the old department of anatomy in Bristo Place For a time he was also assistant surgeon to Chalmers Hospital, and for many years he was consulting surgeon to several of the Border hospitals, notably Hawick and Galashiels He was surgeon to the East of Scotland Civil Service Nursing Home from its inception till his death

He was elected president of the Royal College of Surgeons of Edinburgh in 1949 During his two years of presidency many reforms in the domestic affairs of the college were carried through, and in public appearances he upheld the dignity of the office with great acceptance He was elected to honorary fellowship of the Royal Faculty of Physicians and Surgeons of Glasgow In 1955 he became president of the Medico-Chirurgical Society and he retired from this post last year

He leaves a widow and a daughter

Most students first met Mr Quarry Wood as their teacher of anatomy, and the regard and affection which so many acquired for him at that stage in their careers was added to when they again met him as a teacher of clinical surgery in their later years He lectured always without a note, and was obviously a master of his subject. He had an orderly mind, and his presentation of any topic made it seem obvious and inevitable

His surgical work, for which many must be grateful, was notable for the skill and ease with which it was done In thirty years I never saw him display any sign of ill temper or irritation, however trying or difficult the operation might be Under the most demanding conditions his manners remained those of a gentleman and never denoted his inner feelings In his contacts with his staff he always showed a punctilious regard for good manners and a certain formality of behaviour which never allowed the use of anything but official titles and practically never of Christian names And at the same time he stimulated both high regard and deep affection, for on rare occasions the kindliness, the simplicity, and the high principles by which he set so much store shone through the veneer of formality that he ever wore, and then his true greatness became evident.

He was a skilful angler To watch this rather slightly built man wading deep in the Tweed and wielding a sixteen-foot rod with ease and precision was to see the true artist at work

Edinburgh surgery is the poorer for the loss of a man of such high principles, and yet he probably never realised how much affection and regard he generated not only in his own immediate colleagues but in medical men all over the world who had only known him as students His conscientiousness and his high sense of duty were obvious to all, but his simplicity and his modesty were only known to his more intimate colleagues, and were the foundations of his greatness

W.A D A

JOSEPH GEORGE EMANUEL

M D, B Sc. Lond, M B Birm, F R.C.P

ON March 3, in his 87th year, Dr J G Emanuel died in Birmingham, the place of his birth and the scene of most of his active life

He was the eldest son of the Rev G J Emanuel, a remarkable minister of the Hebrew congregation, and went to King Edward's School and later to the Queen's and Mason Colleges for his training in medicine In 1891 he took the B Sc Lond and he qualified in 1896, four years before the University of Birmingham was established After a period of residence in the City of London Hospital for Diseases of the Chest he obtained the M B Lond with honours, and the M D in 1901, in the following year he became M B Birm. and M.R.C P He was elected F R.C P in 1921 An original member of the Association of Physicians, which was founded in 1907, he served on the committee from 1931 to 1933 and was president in 1939

In 1900 he had returned to Birmingham as pathologist to the General Hospital, where his duties included the post-mortem work, histology, and bacteriology In 1903 he was elected physician to the Queen's Hospital, and he served it with distinction and wholehearted devotion until he retired at the age-limit in 1931

In 1930 the death of Laurence Ball left vacant a chair of medicine in the University of Birmingham, and with some difficulty Emanuel was persuaded to undertake the responsibility for four years, his innate modesty made him doubt his fitness for the work and he was surprised and pleased to find that he had the unanimous support of his colleagues and that the students liked him After retirement from the chair he gave much time to the exacting work of planning and building the new Medical School at Edgbaston and the Queen Elizabeth Hospital Until recently he was a valuable member of the house-committee of the hospital

A P T adds the following tribute to his first medical chief

Emanuel belonged to the generation which witnessed the dawn of the modern revolution in medicine and he told me more than once that he considered he had been exceptionally lucky in the date of his birth Never, he felt, would there be a period so interesting for a physician as that through which he had passed Trained at a time when clinical medicine was based largely on an empirical philosophy which regarded experience as the only source of knowledge and when the lack of scientific methods of investigation and of adequate statistical control of therapeutic trials exposed physicians to the temptations of oracular opinions with insufficient rational evidence to support them, Emanuel in his 30s accepted the challenge of the new situation He carried out for instance some of the first Widal reactions to be done in the Midlands and introduced the sphygmomanometer to his wards and later the electrocardiograph That eager delight in every fresh advance stayed with him to the end and made him a delightful companion long after he had retired from practice, for he never lost his critical sense, and his comments on what seemed to him spurious were flavoured with a quiet and at times slightly cynical wit His courage in adversity was remarkable After an amputation of a foot two years ago he painfully taught himself to walk again and never referred to his disability To his kindness there was no end, but of that as of his courage no mention was permitted During the troubled period of Hitlerian persecution of the People of his faith Emanuel was always at the service of his unhappy, displaced brethren and many of them owe to him the reconstruction of shattered lives To us in Birmingham he has left the inspiration of a fine and devoted life Stevenson's judgment of a physician as the flower of our civilisation may to some seem over-generous, men like Emanuel, however, suggest that it is sometimes true

ROBERT KING HOWAT

M B Glasg, F R C S, F R F P S

Dr Howat, honorary consulting surgeon to the North Riding Infirmary, Middlesbrough, died at his home in Highgate, London, N 6, on Feb 9 at the age of 87

He studied medicine at the University of Glasgow and at the London Hospital After qualifying in 1892 he held a demonstratorship in anatomy at the School of Medicine in Edinburgh and later house-appointments at the Dorset County Hospital and the Wolverhampton and Staffordshire General Hospital Soon after he took the F R C S in 1896, he returned to Glasgow where he became extra dispensary surgeon at Glasgow Royal Infirmary and interim lecturer in anatomy at Anderson College In 1899 he was elected F R F P S Two years later he moved to Middlesbrough, and soon afterwards he was appointed to the honorary staff of the North Riding Infirmary where in due course he had charge of the X-ray, eye, and ear and throat departments He was also surgeon to the Chaloner Hospital at Guisborough He was called to the bar in 1914

In 1932 he retired and moved to London For a time he was an honorary demonstrator of anatomy at King's College But ill health forced him to restrict his activities He had published papers on such varied subjects as minor injuries of the foot, postpartum hæmorrhage, and the health of the private-school child, and in his retirement, though often confined to bed, he began work on his book *Osteology for Dissectors*, which was published in 1950 He leaves a widow

Dr J G GREENFIELD

Although I met Dr Greenfield first in 1933 and have been in contact with him on many occasions, it was only during the last five years that I came to know him more closely through joint work, and learned to admire his enormous capacity for work, his profound knowledge of neuropathology in all its historical and cosmopolitan ramifications, his modesty, and his friendly sense of humour Although he was firmly rooted in the classical past of his specialty, it was impressive to watch him recognise that a new era had commenced with the development of histochemical and ultramicroscopic methods

In a recent memoir on Thomas Mann his daughter called her father's last year a " year of grace and harvesting despite resolute hard work " One is tempted to apply similar words to the closing period of Dr Greenfield's life He certainly did enjoy hard work more than ever, and his harvest has been considerable It is tragic that he did not live to see his *opus magnum* published

A M

A memorial service will be held at noon on Thursday, March 20, at St Martin-in-the-Fields

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Diary of the Week

MARCH 16 TO 22

Sunday, 16th

COLLEGE OF GENERAL PRACTITIONERS
11 A M *Midland Faculty* (Powick Hospital, Worcester) Dr Denis Williams What Keeps Us Conscious

Monday, 17th

UNIVERSITY COLLEGE, Gower Street, W C 1
5 P M Dr J D Judah Oxidative Phosphorylation, Interpretations and Mechanisms (Second of two lectures)
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
9 30 A.M Prof A K Basu (Calcutta) Clinico-Pathological Study of Cases of Pulmonary Tuberculosis Treated by Antibiotics and Pulmonary Resection
4 P M Dr K G Lowe Acute Renal Failure
HUNTERIAN SOCIETY
8 30 P M (Talbot Restaurant, London Wall, E C 2) Dr J A Dudgeon, Dr W H Kelleher Poliomyelitis

Tuesday, 18th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Pathology* Dr Israel Chanarin, Dr D L Mollin, Miss B B Anderson Folic Acid Deficiency Dr J L Stafford Hypoplastic Anæmia in Infancy Dr Sidney Shaw, Dr R A M Oliver Primary Hæmorrhagic Thrombocythæmia
INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W C 1
5 30 P M Prof N F Maclagan Biochemistry of Coma
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
5 30 P M Dr Imrich Friedmann Microscopical Anatomy of the Ear
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr K I Nissen Orthopædic Aid for Spastic States

Wednesday, 19th

ROYAL COLLEGE OF SURGEONS, Lincoln s Inn Fields, W C 2
4 P M *Faculty of Anæsthetists* Prof W D M Paton Mechanisms of Transmission in the Central Nervous System (Joseph Clover lecture)
ROYAL SOCIETY OF MEDICINE
5 P M *Comparative Medicine* Dr D D Lawson, Dr R N Smith Mr Arthur Naylor Comparison of Disorders of the Intervertebral Disc in Man and Animals
8 15 P M *General Practice* Dr Harold Stewart, Dr A A Mason, Dr C A H Watts An Appraisal of Hypnotism in General Practice
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr R Winston Evans Certain Aspects of the Pathology of Ovarian Tumours
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W 1
8 15 P M Prof Robert Kark (Chicago) Bright s Disease Then and Now
NOTTINGHAM MEDICO CHIRURGICAL SOCIETY, 64, St James's Street, Nottingham
8 30 P M Dr George Day Fascination of Tuberculosis

Thursday, 20th

ROYAL SOCIETY OF MEDICINE
4 45 P M *Dermatology* Dr J Martin Beare, Dr G B West, Mr K W Head Mast Cell Disorders
BRITISH INSTITUTE OF RADIOLOGY, 32 Welbeck Street, W 1
8 P M Dr L F Lamerton Examination of the Clinical and Experimental Data Relating to Possible Hazard to the Individual of Small Doses of Radiation (Presidential address)
WEST LONDON MEDICO CHIRURGICAL SOCIETY
8 P M (Star and Garter Hotel, Putney Bridge, S W 15) Mr A Dickson Wright Famous Operations in History
HYPNOTHERAPY GROUP
8 P M (1, Wimpole Street, W 1) Dr Thomas Main, Dr Denys Kelsey Agoraphobia
UNIVERSITY OF BRISTOL, Royal Fort, Bristol 8
8 30 P M Mr T E Cawthorne Facial Palsy (Patrick Watson Williams lecture)
MANCHESTER MEDICAL SOCIETY
8 P M *Anæsthetics* (Staff House, University of Manchester) Dr J Alfred Lee Experiences with Extradural Analgesia

Friday, 21st

ROYAL SOCIETY OF MEDICINE
5 P M *Epidemiology and Preventive Medicine* Air Commodore C A Rumball, Dr H E Parry Dr J D Abbott Dr K B Rogers Management of Carriers of Bacteria Causing Intestinal Diseases
8 15 P M *Radiology* Mr Harvey Jackson, Mr J Jackson Richmond Pituitary Tumours
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3 30 P M Mr G H Howells Cancer of the Larynx

Notes and News

JAMES SPENCE MEMORIAL

In response to the appeal for a memorial to the late Sir James Spence, £4840 was subscribed

From this a gold medal will be awarded by the British Pædiatric Association (every three or four years or less frequently) for outstanding contributions to the advancement or clarification of pædiatric knowledge For the publication of Spence's collected writings a sum of money has been given to the council of King's College, University of Durham Contributions from Australia will be used to cover the cost of modelling and casting in bronze a portrait head of Sir James, to be placed in the children's department of the Royal Victoria Infirmary, Newcastle upon Tyne, and ultimately in the new Children's Hospital when that is built A replica of the sculpture has been presented to the Australian Pædiatric Association, whose foundation was in part stimulated by his visit in 1948 The residue of the fund will be handed to the council of King's College for the creation of a prize in pædiatrics open annually to students, for " an essay of not more than 3000 words on any subject related to pædiatrics which has excited his or her interest and observation during undergraduate studies "

THE FIRST McMURRAY LECTURE

The late T P McMurray was professor of orthopædic surgery in the University of Liverpool from 1939 to 1947, and a lectureship in his honour was established in 1955 It is fitting that the first lecture [1] should have been given by Prof Bryan McFarland, his successor, and that it should deal with his life, work, and personality

McMurray was trained by Robert Jones, and succeeded him as director of orthopædic studies in the University of Liverpool in 1933, in 1939 he was appointed as the first professor Though he played a great part in building up specialist orthopædic services, he strongly advocated their retention in general hospitals, and pressed for undergraduate instruction in the subject

He was impatient of frills, Professor McFarland tells us, and would say " You mustn't do it " rather than " under all the circumstances it might be inadvisable to proceed in such a way "—which earned him a reputation for gruffness His surgery, too, was direct and purposeful He was cautious, or " canny ", with such innovations as the use of metals in bone, and he stuck to his beliefs ' To his friends he sometimes seemed intransigent, to his critics stubborn, and to his enemies impossible He was of an age of independent authority and independent responsibility " His operation of osteotomy for osteoarthritis of the hip has proved effective, though the reason why it relieves pain is not obvious, and it is receiving renewed attention now that some arthroplasty operations have proved disappointing He wrote books, but his influence was exerted mainly by direct precept, " for those who came under his spell its effects will last for ever "

GUY'S HOSPITAL DENTAL SCHOOL

The annual clinical meeting of Guy's Hospital Dental School was held on March 1 In the year since the last meeting there have been few sensational advances in dentistry, but it has been a period of steady improvement in methods The novelty which aroused the greatest interest was an instrument for cavity preparation shown by Mr W A Vale This is an air-turbine-driven handpiece, capable of speeds up to 50,000 revolutions a minute, which attracted a good deal of attention when it first appeared at the International Dental Congress in Rome last year Diamond or tungsten-carbide burrs, rotating at high speeds, can cut cavities in teeth rapidly and almost painlessly, and the ' Borden Airotor ', as the instrument is called, has many advantages over the conventional electric motor, although at the moment it is rather more costly At least one patient upon whom the airotor was used said that he was going to ask his own dental surgeon to buy one at the earliest possible opportunity

A further reminder of the International Dental Congress was the photographic exhibit which the hospital sent to Rome last year This display included portraits of eminent Guy's dental surgeons of the past, and a series of photographs illustrating the various stages in the career of a dental student

The dental photographic department, under the able and enthusiastic direction of Mr A D Robinson, who produced this exhibit, showed some of the techniques used in dental photography Colour photographs of the mouth—not one of the easiest regions of the body to represent satisfactorily—have now been brought to a high degree of technical perfection by Miss Whiteley and her assistants Mr Robinson showed a film, entitled *Becoming a Dental Surgeon*, which he made for exhibition to senior schools to give prospective dental surgeons some idea of hospital life

Towards the end of last year, Prof M A Rushton's department of dental medicine vacated its old and cramped quarters for new and well-equipped rooms in the old pathology block behind the Dental School, and the new premises were on view publicly for the first time on Saturday The work on which the department is engaged includes an interesting study by Mr A C Kerr on the antibacterial action of human saliva In the afternoon, Professor Rushton presented his usual annual review of interesting and unusual cases referred to him by dental practitioners, the packed lecture theatre showed what a popular feature of the clinical meeting this lecture has become

SCOTTISH HOSPITALS ENDOWMENT RESEARCH TRUST

The Trust issued its first report a year ago [1] The report for 1955–56 [2] contains a list of those to whom grants have been awarded The Trust is now prepared to consider paying travelling expenses to enable applicants to attend scientific meetings in the United Kingdom, provided that the expenses are directly connected with a project supported by the Trust

AMATEUR'S LONDON

Against professionals, such as the police and taxi-drivers, most Londoners show up badly when asked to direct a stranger, say, to the Soane Museum or the Equadorian Embassy This is not for lack of interest in the topography of London, as anyone will know who has listened in grateful bewilderment to the eager but divergent instructions offered under the general direction of the conductor by a posse of aroused bus passengers once the ice has been broken But each Londoner tends to have a specialised knowledge of the parish where he lives and/or works Outside these precincts he is no less vague, indeed often a good deal vaguer, than the intelligent visiting foreigner with a reliable *Baedeker* or *Guide Bleu* Now he has been offered a guide book [3] of his own by Mr Colin Hunt, who for over ten years has been coaching taximen for the exacting examination they have to face for their licence The book contains, among other useful information, 8 maps of the West End and City (17 in to 1 mile) and over 30 classified lists which alphabetically cover every facet of life from " air transport " to the " University of London ", giving not only the address of each institution but also terse instructions on how to locate it Motorists will study with interest Mr Hunt's 500 routes which criss-cross London, making due allowance for traffic congestion, from such unlikely points as the Mildmay Mission to the Tavistock Hotel and the Society of Friends Meeting House to Shell-Mex House It seems curious that this particular book should be published in Edinburgh

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University of Oxford

On March 1 the degree of D M was conferred on the following

G N Chandler, *H M Lloyd *Ursula F Rowlatt

*In absentia

University of Birmingham

Dr D A Heath has been appointed lecturer in pathology

Royal Institute of Public Health and Hygiene

The Harben medal has been awarded to Sir Howard Florey and the Smith award to Dr Charles White.

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[1] The Life and Work of Thomas Porter McMurray By Bryan McFarland Liverpool University Press 1958 Pp 12 5s

[1] See *Lancet* 1957 i 676

[2] Scottish Hospitals Endowment Research Trust Annual Report and Accounts, 1955 56 H M Stationery Office 1955 Pp 12 1s

[3] Here it is Knowledge of London Edinburgh C J Cousland & Sons 1958 Pp 274 15s 6d

Christian Medical Fellowship

On Wednesday, March 26, at 8 15 P M at a meeting of the Christian Medical Fellowship at the Royal Empire Society, Northumberland Avenue, London, W C 2, Mr D MacG Jackson will speak on moral responsibility in clinical research

The Wolfenden Report

The Institute for the Study and Treatment of Delinquency is to hold two conferences this year on this report

The first of these will deal with prostitution and will take place at Bracklesham Bay Hotel, Sussex, from April 18 to 20 The speakers will include Dr T C N Gibbens and Dr Edward Glover Further particulars may be had from the Institute, 8, Bourdon-street, London, W 1

Carlsberg-Wellcome Travelling Research Fellowships

The directors of the Carlsberg Foundation, in Copenhagen, and the Wellcome Trustees, in London, instituted these fellowships in 1957 to encourage friendly cooperation, on an exchange basis, between Danish and British research-workers in any branch of the natural sciences which has a bearing upon human and animal medicine One fellowship annually is awarded to a candidate from the United Kingdom for a year's work in Denmark, and one annually to a Danish candidate for a year's work in the United Kingdom

The stipend may range from £800 to £1200 per annum (or the equivalent sums in Danish kroner) for whole-time research Travelling and some incidental expenses are provided in addition It is intended that the second appointments shall be made in respect of the academic year beginning in September, 1958

Inquiries about these fellowships from candidates in the United Kingdom should be addressed to the scientific secretary of the Trust, 52, Queen Anne Street, London, W 1 There is no form of application, but candidates should submit a full *curriculum vitæ*, together with details of their research proposals and a supporting letter from a senior scientist who is familiar with their work Completed applications must be submitted before April 30

Medical Society of London

At the 178th anniversary dinner the toast of The Society was proposed by Admiral of the Fleet the Earl Mountbatten of Burma The medical profession, he said, had played an immensely valuable part in the success of the South East Asian campaign In 1942 before he went out to Burma the annual sickness-rate of the Army was 185%, and for every battle casualty there were 120 sick With the Prime Minister's agreement a medical advisory division was created consisting of British Army, Navy, and Air Force doctors and an American Army doctor—all specialists in tropical diseases Thanks to their activities and the wonderful work of the medical services already in SEAC, the sickness-rate had fallen to 50% in 1945 The position had so changed that we were able deliberately to choose unhealthy areas in which to fight—areas in which the Japanese suffered terrible losses from disease but in which we were able to keep our men healthy by our newly developed protective measures "I know of no other case where medical science played such a vital role in turning victory into defeat as in Burma" He believed that, despite the closure of Naval hospitals, including that of the Royal Naval Hospital, Chatham, which has recently been announced, the Royal Navy still offered as good a career as ever to doctors, with prospects which would probably be better

Sir Cecil Wakeley, the president, thanking Lord Mountbatten, said that the society was honoured by the presence of one of the key men of the nation He went on to review the activities of the year, and reported that all the meetings had been well attended Subjects already discussed ranged from leadership (General Sir Brian Horrocks) to life in a cold climate (H E Lewis and J P Masterton), and those in prospect included tropical medicine in Great Britain, the early years of anæsthesia, and new lamps for old in cardiology He expressed the society's warm thanks to the registrar, Mr P Minter, and his wife, for their continued help

In his welcome to The Guests, Mr E G Muir spoke of Lord Mountbatten—First Sea Lord and last Viceroy of India—as a man who had brought to the game of polo the dash of the destroyers and the overall command of the chiefs of staff Dr T F Fox, who responded to this toast, described the society's annual dinner as always among the most agreeable of London's medical functions

British European Airways

The medical consultants' panel of this corporation now consists of

Dr D Evan Bedford, consultant cardiologist, Dr Kenneth Black, consultant physician in diseases of metabolism, Mr J D Cambrook, consultant dental surgeon, Mr W D Coltart, consultant orthopædic surgeon, Dr James Cyriax, consulting physician in physical medicine, Sir Daniel Davies, consultant physician, Air Vice-Marshal E D D Dickson, consultant otorhinologist (aircrew), Lord Evans, consultant physician, Dr Keith Jefferson, consultant radiologist, Mr Rodney Maingot, consultant surgeon, Sir Archibald McIndoe, consultant in plastic surgery, Mr Wylie McKissock, consultant in neurological surgery, Dr Swithin Meadows, consultant neurologist, Mr C Naunton Morgan, consultant in general surgery, Mr H Osmond Clarke, consultant orthopædic surgeon, Dr J D Robertson, consultant pathologist, Mr B W Rycroft, consultant ophthalmic surgeon, Mr W G Scott-Brown, consultant otorhinologist, Dr Cedric Shaw, consultant physician in diseases of the chest, Dr W A H Stevenson, adviser on clinical psychiatry, Dr E B Strauss, consulting physician in psychological medicine, Dr H J Wallace, consultant dermatologist, and Sir Harold Whittingham, consultant in aviation medicine

The director-general of B E A medical services is Dr A Buchanan Barbour

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Sir Hans Krebs has been awarded the gold medal of the Netherlands Society for Physics, Medical Science, and Surgery

A refresher course for general practitioners is being held at the Southern Hospital, Dartford, Kent, on Fridays, at 2 45 P M, from April 11 to June 20 Further information may be had from Dr J C Hogarth at the hospital

On Thursday, March 20, at 5 30 P M, at the Fountain Hospital, Tooting Grove, London, S W 17, Dr J W Millen and Dr D H M Woollam will speak on the experimental production of malformations of the brain

On Friday, March 21, at 8 45 P M, at a meeting of the Leicester Christian Medical Association in the Leicester Royal Infirmary, Dr Edward F Griffith will speak on psychotherapy and marital disharmony

A semi-permanent exhibition on moniliasis will be held from March 31 to April 25 at the Institute of Dermatology, Lisle Street, London, W C 2

The Ministry of Power has issued the *Digest of Pneumoconiosis Statistics for 1956* (obtainable from H M Stationery Office Pp 20 3*s*)

The proceedings of the conference on the Challenge of Mental Deficiency, held by the National Association for Mental Health in Manchester last November, may be had from the Association, 39, Queen Anne Street, London, W 1 (pp 58 5*s*)

The Board of Registration of Medical Auxiliaries have lately added to the registers which they publish a register of audiology technicians and a register of technicians in venereology Doctors may obtain free copies of these from the Board, B M A House, Tavistock Square, London, W C 1

CORRIGENDA *Essential Fatty Acids, Lipid Metabolism, and Atherosclerosis*—In the paper by Dr Laurance W Kinsell and his colleagues (Feb 15, p 331) table IV should have been headed findings in a woman, aged 19, with no evidence of vascular disease

Ataralgesia—We unfortunately introduced a mistake in Dr Hayward-Butt's letter of Feb 15 The sentence "It is quite possible that levorphanol will prove as satisfactory as amiphenazole" should have read "It is quite possible that *levallorphan* "

Appointments

BAIRD I McL, M D St And, M R C P part time consultant physician, Barnsley group of hospitals

BAKER, C H J, M R C S, D P H school M O and assistant M O H, Exeter

DAVIES D K L, M B Wales, D M R D consultant radiologist, Cardiff H M C group

KINDER C H, M CHIR Cantab, F R C S assistant surgeon, genito-urinary department Guy's Hospital, London

MEEK J C, M B Glasg, D M R consultant radiologist Newport H M C group

MURRAY C J B, M S Lond, F R C S consultant surgeon Royal Masonic Hospital London

SIEGLER JOSEPH M B Lond, F R C S D L O part time consultant otorhinolaryngologist Liverpool Ear, Nose and Throat Infirmary, Clatterbridge Hospital and Aintree Hospital

TUCKWELL, I G, M CH Oxon F R C S consultant surgeon Royal Masonic Hospital London

WALTERS GLYNDWR M D Brist, M R C P consultant pathologist Wolverhampton group of hospitals

The Lancet · Saturday 22 March 1958

WHAT SETS THE GOALS OF PUBLIC HEALTH?*

Sir Geoffrey Vickers
V C, M A

I ask what sets the goals of public health I do not ask how we choose them, for manifestly our choice is only one element in a manifold process When we open our eyes to the scene around us, we find goals already set Policies are being implemented, institutions are in action with all the historical momentum of buildings and establishments Men are in mid-career. Budgets, even budget headings have acquired prescriptive rights This dynamic configuration is resistant to sudden change So the most obvious answer to my question springs to mind at once History sets the goals of public health We influence them no more and no less than we influence the course of history

The process of interaction and mutual adaptation which we call history is an obscure, though familiar, mystery Looking into the future, we see a widening vista of possibilities Tomorrow is almost committed, but next year, ten, twenty years hence, what might not be possible? Yet looking into the past, the vista seems to narrow from past to present We see a thin line of actualities detaching itself from all that might have been, and those who will some day look back over what is now the uncommitted future will see the same Of all that competes for realisation, only a tiny fraction is realised, and in the process it excludes a host of alternatives The eternal enigma of history is, "Why from all these possibilities did these, rather than any of the others, come to birth?" Somewhere in the answer to that question lies, among many other things, the scope and meaning of human initiative

Among the forces which make history, one of the most obvious is human need Some would say that need sets the goals of public health New needs emerge and evoke the measures which will satisfy them At any moment, with a more or less significant time-lag, the goals of public health reflect the dominant needs of its time and place

This statement is not so simple as it looks The needs which evoke response are those which are recognised as needs, and this process of recognition has odd features Our culture accepts some conditions of living which in other epochs would have moved slaves to rebel—such as going to work on a rush-hour subway, and on the other hand insists on others which other epochs never thought of—such as having its bread wrapped in 'Cellophane' Why this particular selection of needs? Again, we cannot satisfy all the needs we recognise Our age, with public-health services more abundant and more active than in any before it, is probably more aware than any other of unsatisfied needs How are they resolved, the conflicts between needs fighting for satisfaction? Are they resolved by human choice? And, if so, by what criteria?

In answering these two questions we discover how significant that time-lag may be In 1946 the British Parliament, with the passing of the National Assistance Act, thought that it had destroyed the last vestiges of that "New Poor Law" which the reformers of 1834 expected to abolish destitution Yet every page of the new statute reflects attitudes which are not responses to the future but protests against the past It is not only soldiers who start each war perfectly equipped to win the one before

Previous ages had neither subways nor 'Cellophane', so they had no occasion to opt for or against them The thought suggests another To some extent at least techniques set the goals of public health For techniques not only enlarge our responses, they mould our expectations

Most obvious is the impact of therapeutic and preventive techniques Pasteur set the goals of public health for many decades ahead Every new technique, by opening a possibility, awakens a need—at least in our Western culture, where in matters of health we have a highly developed sense that whatever is possible for any should be available to all.

Therapeutic and preventive techniques depend on industrial techniques Apart from the techniques of the pharmaceutical industry, on which all chemotherapy depends, the engineering industry is the main executant of sanitation Equally important are administrative techniques Large-scale public works are possible only in societies which are capable of administering them and of collecting and spending the money they involve, societies moreover which are tolerant of high taxation and of land requisition and which are accustomed to think in terms of social and geographical areas commensurate with the problems involved

These factors also limit the goals of public health. As we, looking back a few decades, see our societies at a stage which, not only did not attempt but could not have attempted much that we regard as a matter of course, so a not so distant future age may see us enmeshed in limitations of administrative vision which we cannot yet discern

These limitations are manifold Every executive authority concerned with public health is limited not only by money and technical skill but by the area of space and the span of time over which it is free to plan, and by its own past experience, which goes far to determine how it shall set about its new problems And apart from these direct limitations, each authority is limited by its own current activity For our powers of attention are limited, and the habit of placing something at the focus of our attention implies the habit of leaving other things in the periphery

Techniques limit us in yet another way A technological age expects to deal with its problems technologically Consider the growing hazard of noise To earlier ages the natural remedy would have seemed to be—to make less noise That, I fear, would seem regressive and defeatist to us So many alternatives are open

We might take to wearing helmets which excluded all noise absolutely Dual—or better, triple—microphones round the helmet could be so devised that they could distinguish and reject sounds, however loud, which came from remote sources, admitting only those which arose nearby We could thus converse in comfort, while the roads roared with machinery and the air screamed with jets The helmets would be bad

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for our hair, but we should not want hair if we were always to wear helmets Medical technology would devise a painless and permanent method of depilating the scalp, and fashion stylists would have greater scope with our helmets than they could possibly have with our hair Each incidental problem would offer a new opportunity for technology

Furthermore, we should have achieved a moral advance in at least two directions By getting rid of our hair, we should have abolished one of those tiresome, hereditary differentials which conflict with our ideas of equality And we should have enlarged the area of human freedom, by giving us new powers of choice in deciding to what we should attend Above all, we should have again eluded the regressive, defeatist solution of saying No The engineers would no longer be threatened by the limitation of what our ears would stand Progress would have burst another barrier

To be exact, we should have avoided saying No in the one field where that word is unacceptable to us Our impoverishment would fall only in areas of life which are—commercially—insignificant.

If this forecast of a brave new world sounds fanciful to you, does it seem any more fanciful than the thought of a technological age deliberately choosing to be less active in order to be less noisy?

So let us add another to our list of goal-setters Ideology sets the goals of public health

Needs, techniques, ideologies—these are names for aspects, dimly understood, of that mutually adaptive process which we call history But among the interacting forces is one, unique and clearly identified—our individual human selves, no mere pointers recording the resolution of external forces but pointers dynamically charged, themselves contributing to the forces they record We must determine our own role, if we are to complete our analysis of what sets the goals of public health

II

This is perhaps the moment to question whether public health has any goals Is it not governed rather by avoiding threats? Let us not confuse ourselves by saying that a threat is only a negative goal The psychologists have wrought havoc with lay thinking by popularising the term "goal-seeking" as if it covered all purposive behaviour It begins now to be widely recognised that threat-avoiding differs from goal-seeking in important ways One of the most important is this If I successfully seek a goal, I shall ultimately find it and then I shall discover whether I really like it But if I successfully avoid a threat, I shall never experience it and so I shall never discover whether it was worth avoiding

Threat-avoiding bulks large in our individual motivation, and I fancy that it plays an even larger part in the collective decisions of larger and less coherent bodies In individual motivation the psychologists tell us how much of our behaviour is directed to avoiding what we recognise, often unconsciously and often wrongly, as a threat The landmarks of political, economic, and social history are the moments when some condition passed from the category of the given into the category of the intolerable The welfare legislation of Great Britain is based on a report which identified "five giant evils" as goals for attack—disease, unemployment, ignorance, squalor, and want I believe that the history of public health might well be written as a record of successive redefinings of the unacceptable

It is safer, none the less, to assume that public health knows goals as well as threats, but it is not safe to assume that these are interchangeable—positive and negative ways of saying the same thing

In any case, goals and threats are not ultimate governors of behaviour, on the contrary, they are the most superficial of all Much of the confusion which surrounds the discussion of ends and means comes from the fact that a "goal" or "end", if it is attainable once for all, is never more than a "means" to maintaining some relationship which must always be sought anew My dinner is a "goal", something I seek and either find or do not find, but it is only a means to maintaining that rate of metabolic exchange which must be maintained through time as long as I live The specific goals we pursue—I will call them objectives—are always means to attain or preserve some relationship, internal or external, which we need or think we need The specific threats we seek to escape are threats to some relationship, events which we think might strain the relationship perhaps beyond repair These continuing relationships I will call norms We seek to maintain them, when we deviate from them, we seek to return But they have thresholds beyond which we may not—or think we may not—deviate without disaster, thresholds which in the clearest cases mark points of no return, and these I call limits

Physiologically, our needs for food and drink and air fall readily under these descriptions They are relationships with the environment, they have an optimal position and they have thresholds beyond which they cannot deviate without disaster Our psychological and social needs, so far as we can discern them, seem to be of the same kind "To be secure," "to be successful," "to be happy" are relationships which no one expects to attain once for all

Health is clearly a norm, not a goal, according to this terminology—a relationship not to be attained once for all but ever to be renewed Disease is a deviation from this norm and includes a series of limits beyond which irreversible change takes place, the most dramatic being death

This is not the normal meaning of health and disease The constitution of the World Health Organisation does indeed define health as a state of complete physical, mental, and social wellbeing and not the mere absence of disease or infirmity But who is to define for each individual that state of multiple excellence which under this definition would constitute health for him? It is easier to equate the norm with the normal and to count as disease only what falls below this assumed level of normality Yet few, I think, would quarrel with the implication of the W H O constitution that health is a form of individual excellence

It is common today to describe human striving in terms of tension reduction, and this serves well enough to describe the norm-seeking and limit-avoiding which I regard as the basic governors of our activity But it is not always remembered that our norms and limits are to some extent self-set The architecture of our expectations determines the operative tensions, whether positive (between what is and what we think "ought to be") or negative (between what is and what we think "ought not to be"), and the process of adaptation consists no less in the redesigning of our own expectations than in the manipulation of our environment

There is an intimate mutual relationship between these two processes The development of the automobile did more than provide us with new means to satisfy our needs It set new needs, new expectations, new norms of mobility, even new limits of unacceptable immobility

The essential character of industrial expansion and the root of its basic instability is precisely that it creates and continually changes the expectations to which it is supposed to minister Commercial advertising is socially significant not as a medium for proposing and indirectly defining the specific objectives through which our expectations can be satisfied, but rather as a means of setting and constantly resetting the expectations themselves

The process by which we set and revise our governing expectations is obscure, largely unconscious and immensely important. Consider in how short a time the United States has developed among a population so large and so diverse that wide conformity of expectation which is understood by the American Way of Life I do not seek to explore that astonishing achievement here It may serve to illustrate the fact that the character and coherence of a society or of an individual personality is largely a function of its governing expectations, the norms and limits which describe its setting as a dynamic system, and that the crucial task of adaptation is the adjustment of this inner architecture so as to maintain effective contact with the environment without losing that inner balance of forces whereby the individual or the society hangs together

The process of history is a process of mutual adaptation Every organism and every society is a dynamic system, an ever-shifting balance of forces, and it has continually to solve a double problem It has to regulate the interaction of its inner forces whereby it hangs together, and it has to regulate the interaction between itself as a whole and its environment Neither configuration is infinitely plastic, each can be changed only within limits and notably within limits of time Thus the creature must learn to find the food it can digest or learn to digest the food it can find, and it survives only so long as it can find a viable compromise between its needs and its opportunities

I invite you, then, to consider our behaviour in the field of public health as one aspect of that historical process in which we are engaged, a process of adaptation in which, consciously and unconsciously, we continually modify both our external environment and our inner system of expectations—behaviour which can be defined at any given moment in terms of the relationships which it is set to maintain and the limits which it is set to avoid, but which is as much and as properly concerned with redesigning its norms and limits as with modifying its external environment It is within this process, still largely blind, that human initiative plays whatever may be its part and thus takes a hand in setting the goals of public health

I hope I have made it clear that I regard the process by which these goals are set as largely beyond our control—largely but not wholly Our conscious contribution, though limited, may be crucial To explore its possibilities, I will consider the kind of situation in which it seems most operative—that is, in the taking of concrete decisions

Suppose someone has to decide whether a particular child, at present neglected and ill-used, should be given institutional care or left in its ill-found home The decision is taken within a framework of half-conscious value judgments as to the relative importance of children's rights and parental rights, the proper limits of official interference, the effect on children of separation from parents at different ages the merits and demerits of institutional as against familial care and so on These judgments reflect the governing expectations of the deciding minds at the time, the norms and limits by which they are regulated, their "setting", if you find it convenient to regard them as dynamic systems

But within this framework of norms and limits there operates a set of practical considerations of a very different kind Is there a place in a suitable institution? Will it be wanted for some other more urgent case? What is the quality of institutional care available here and now? The answer to the particular case may well be given by these practical considerations alone

But the particular case is by no means all that is being decided. It serves to confront today's expectations with today's possibilities and thus to release into the stream of policy-making the consciousness of a disparity, a maladaptation The institutions available now were built in response to the felt needs of an earlier decade Today's revised intuitions of need will not be realised in terms of buildings, budgets, staff, training, and the rest for some decades to come They are already muted by the past, for our inherited institutions have themselves contributed to our current ideas of what institutional care connotes, and our revised ideas, on the way to realisation, will have to fight for their lives against other equally valid intimations in totally different fields, which compete with them for resources, space, skill, and attention Yet it seems to be through the deciding of concrete cases today that we crystallise the insights and the discontents which mould the standards and the institutions of tomorrow

I have taken this cursory look at the historical process in the hope of discerning where human initiative comes in So far the answer is far from clear All decisions, it seems, are choices between a limited number of specific alternatives, all sometimes highly unwelcome They challenge us first to distinguish these alternatives and to evaluate them They challenge us further to inquire how those choices came to be posed and to consider through what inner and outer adjustment they may be answered more acceptably in future The possibilities in this second field are, I think, the wider, and it is chiefly through them in my view that we have the power to take a hand in setting the goals of public health, and not the power alone but also a duty and a need of unusual intensity today

III

For public health in our Western culture would seem to be at a crossroads For a hundred years it has been concerned mainly with the age-old threats which beset a species not too firmly established on the Earth—the threat of deficiency in our basic metabolic needs for enough food and rest, the threat of competition from the only other genus which still disputes with us for mastery of the planet the bacteria In its battle with deficiency and with infection public health achieved spectacular success True, that success does not look so final today as it did twenty or thirty years ago The world still contains many undernourished people and it is not clear that their numbers will be less a hundred years hence Bacteria and viruses become resistant to our present methods of attack and continually threaten us anew The fact remains that Western societies are less preoccupied than ever before with the control of deficiency diseases and infectious diseases

They are, however, no less concerned with disease Metabolic disorders, mental disorders, disorders of excess rather than deficiency, have risen in importance as others have declined and with these we are at present less well equipped to deal Our hazards from excess range from excessive nuclear radiation, through excessive smoking to the excessive consumption of ice-cream—products which have in common the fact that their superabundance is our own doing Even the still obscure concept of "stress" as a cause of mental ill health connotes excess—the impact of more challenge than the organism is able to bear

A technological age was well equipped to partner public health in its attack on the deficiency diseases and the infectious diseases Even where the new hazards were partly the creation of industrialisation, as in the growth of mammoth cities, industrialisation had the tools to remedy its own defects It was as much at home providing a water-supply and a sewerage system as in building a hydroelectric power station or an arterial road It was possible for Lewis Mumford in his *Technics and Civilisation* to describe the evils of industrialisation as merely features of an eotechnic age

Today it is far from clear that a technological age is as well equipped to partner public health in the next stage of its journey On the contrary, it is likely in my view that the requirements of public health will cut ever more sharply across the valuations of an industrial age What matters most to human wellbeing in the coming decades may well be conditions which industry cannot provide and is in fact chiefly instrumental in denying

These changes will affect every aspect of public health

Public health, as I see it, has three main concerns—with health services, with health conditions, and with the concept of health itself In all three fields it faces important tasks of revaluation

In Britain the introduction of a national health service has helped to clarify our thinking about health At one point it was widely, if half-consciously, held that a health service was a self-limiting service When the demands of health were fully met, there would be nothing more to do Indeed, better preventive services might in time reduce the total resources needed to provide optimum health for all It is clear, I think, that health services are not self-limiting in this sense The amount of effort which can plausibly be devoted to the health of the individual and the community increases with every scientific development and will, I think, increase indefinitely Thus the services which might be provided may well continue to exceed, perhaps by an ever-increasing margin, the services which can in fact be provided, since the total will be limited by the amount of resources available, having regard to conflicting demands Consciously or unconsciously we shall still have to decide what is to be the total volume of resources devoted to public health and how it is to be distributed between different services, different needs, and different classes of beneficiary—for example, between the young and the old These decisions will grow harder, not easier, with the passage of time

Public health has always been especially concerned with preventive medicine, and here its function has been to establish the conditions of health primarily in the physical environment but also in the structure of society and of the individual personality To change, for example, social attitudes towards mental illness or individual attitudes towards prenatal and postnatal care is to change the conditions of health, no less than to lay a water-main Here it would seem that a much wider field is opening

Current American culture is sometimes criticised by American social psychologists on the ground that it builds up and sanctions too many expectations which it does not allow to be satisfied and thus produces more frustration than most people can safely take However this may be, it is clear that the culture and structure of society, including the many subcultures of which it is composed, set conditions which are potent for good and ill These conditions are not under the control of public health but they are not beyond its influence and its criticism

For public health has a unique opportunity, as well as a duty, to clarify our understanding of health and disease and hence our attitude towards it, and this field clamours to be further explored Even the ætiology of those disorders which have hitherto been most prominent is far from fully understood, still more obscure is that of the diseases which claim priority today The distribution of disease, even within the crude categories of our present statistics, is full of oddities In Britain, though infant mortality has vastly declined over the past fifty years, the relative differential between the rates in different income-groups has not been reduced but has, if anything, increased Why? Schizophrenia is known to have a genetically predisposing cause, yet its reported incidence in the lowest income-group is many times that in the highest Why? Such challenging enigmas could be multiplied, I expect, among American statistics, as among British

These thoughts arise only from the indices we at present use But we have no reason to think that our present classifications of people are the most significant We badly need a more adequate classification of human types—and perhaps of human situations also

This again may give us a new idea of the conditions of health We already know, though it is easy to forget, that a " society " at any moment of time contains people of two sexes and all ages, and that the health of each of these is a condition to be preserved through the span of a lifetime Add to this that these people consist not merely of an " admired type ", and varying degrees of deviation from it, but of a wide variety of types, each of which can claim the respect we accord to the normal To do justice to all these diverse claims calls for a concept of the conditions of health more penetrating than any we use now

So let me add another answer to the question which we are asking I would like to think that in so far as the goals of public health are consciously set, they will be set increasingly by practitioners of public health and especially by physicians, epidemiologists, and social scientists working together, with the more abundant techniques and data now available to us, to disentangle more clearly the nature of that dynamic balance which we should recognise as health and the conditions which favour or threaten it

IV

There are, I suggest, three contributions which public health can thus make to the setting of its own goals It can evaluate health by the criteria which we currently use It can criticise these criteria and thus help to deepen and refine them And it can explore those processes of decision by which public-health policy is defined and implemented

The first is a familiar function Public health is at present measured largely by statistics of mortality and morbidity Even these rough indices, as I have already mentioned, disclose differences between localities and categories of people and changes with time which we cannot explain and which challenge us to research Moreover, this information, at least in Britain, is analysed today under categories which are almost certainly less adequate than they need be This is serious, for the categories under which information is gathered are immensely important. They not only influence what we think about, they limit what we can think about

There is thus much to be done in interpreting our simplest indices and in refining the tools and the methods whereby we work on them

Next, there is much scope for refining those criteria of breakdown which we regard as indices of ill-health individual or social Already we use many beyond those basic figures of mortality and morbidity which not long ago would have seemed an adequate measure of public health Alcoholism and drug addiction, crime and perversion, are readily used as indices of breakdown, but how to interpret them? Shall we seek the cause in the nature and history of the individual or in the structure of society? In reaction against the long centuries in which the criminal, the drunkard, the addict, the pervert were regarded as enemies of society, we tend today to assume that they are its victims Fromm and Kardiner have used such statistics to impugn the health not of the individuals concerned but of the society which destroyed them

Clearly, these indices and their interpretation are the concern of public health Clearly, too, their interpretation is more complex than a decision whether they indict the individual or his society, for the interaction between the two is far too subtle and involved to permit any such simple alternative

And here, I think, we are helped by another important change in our approach to health It seems to me that Western medicine is at last getting around to the question which patients have always asked but which hitherto only witch-doctors have taken seriously This is the question—"Why me?"

> Smitten by accident or disease, the savage, as I understand, asks—"Why me? Granted that boughs fall and snakes bite, why should I be the victim, rather than another?" The question would have seemed trivial to the public health of only a few decades ago Suffice it to eliminate, so far as may be, the risks from falling boughs and biting snakes or their equivalent in our day What matter whether A or B is the unlucky one? It makes no difference to the statistics Yet medicine has always known that immunity and vulnerability are in some measure characteristics of the individual In its attack on the infectious and deficiency diseases, medicine is increasingly concerned to build up the inner immunity of the individual, rather than to eliminate the risk from the environment, and the study of individual variations in immunity is an increasing part of medicine's activities
>
> Vulnerability is the opposite side of the same penny The study of psychosomatic disease leads medicine to view an increasing field of illness as highly individual behaviour, the response of a particular person to a situation to which he is vulnerable Even having an accident is coming to be regarded as a form of such behaviour The concept of accident-proneness plays an important part in industrial medicine and its exploration provides ever more material to answer the question—'Why me?"

The concept of immunity and vulnerability as a characteristic of the individual applies no less to mental health and mental disorder and may find here its most important developments We assume that here also there is need of a dual approach—on the one hand, to reduce the hazards of the environment, on the other, to increase the immunity of the individual But we know much less about the meaning of either term "Stress", in the psychiatric as distinct from the physiological sense, is a very imprecise concept, and equally unsure is our understanding of the conditions which make the individual relatively vulnerable or immune to it Even a small enlargement of our understanding here would alter our concept of health

In the field of mental health it seems unlikely that we shall suffer in the near future from lack of hazards It is the more important that we should get a better understanding of the nature of immunity This, it would seem, is a function of the way in which the individual organises his experience on the one hand and his expectations on the other—if you will allow that word "expectations" to stand for all those norms and limits which define the setting of his system The two must be so related that the individual can remain internally coherent and externally effective—I would say "adaptive", if that word had not acquired so one-sided a connotation

Psychiatric literature is full of warnings against allowing our governing expectations to diverge too sharply from the realities of the world in which we live Socially, it may be even more disastrous if they diverge too little, for it is precisely through our sense of this divergence that we exercise over event whatever initiative we can win Every adaptive society must have its protestants, for protest is the mainspring of any adaptation that is not purely passive And since the protester gets more than his share of stress, he needs more than his share of immunity

We need, then, a concept of health which will take account both of the individual's ability to live in his society without breakdown and of his ability to resist its pressures We are still so far from this that laymen at all events do not clearly distinguish the immune from the well-adapted or even from the conformist. Yet, if we had an adequate idea of what adaptation means, we should, I think, recognise the distinction as crucial The agents of adaptation are not those who are commonly called well-adapted, still less are they the conformist, they are those who can carry within themselves without injury a more than usually large measure of tension—tension between the norms of individual and social experience, between the "is" and the "ought to be", between the present and the future, in a word, those who have a high degree of immunity to the pressures which threaten our mental health I have no doubt that such a concept of health and its conditions would incidentally give a new clarity to our understanding both of individual freedom and of the process of democracy, for both freedom and democracy seem to me to be limited in extent and quality by this elusive factor

Finally I suggested that it was within the field of public health to explore those processes of decision whereby the policy of public health is defined and implemented These processes are important, because in them the process of adaptation breaks the surface of consciousness and becomes open to analysis at a new level If we observed the behaviour of officials and politicians, of committees and pressure groups, in the making of some policy, might we not get some more precise insight into the way in which the disparate forces I have noticed combine to set the goals of public health?

Such a research, which would be difficult to design and to execute, would, I think, land us in successive areas of doubt, each more recalcitrant but also more fruitful than the one before

First, we should find, I hope, that the decision which came out of the deciding minds bore some relation to the information which went in, and we should confront the problem how to make available to policy-makers, predominantly lay, the knowledge and attitudes of rapidly expanding sciences

Secondly, we should find that the decision which emerged was a choice between a few specific alternatives, and we should be led to ask how these alternatives were selected and why others were ignored We should encounter the enigma of attention

Thirdly, we should observe that the alternatives between which the policy-makers chose were disparate In that budgeting of resources which underlies all decisions, they have to weigh against each other short-term proposals and long-term proposals, preventive proposals and therapeutic proposals At one level a pædiatric project is competing with a geriatric one At another level a whole public-health programme is fighting for a place in the national budget with something as disparate as a hydrogen bomb How in the world do the policy-makers weigh against each other alternatives so different in character?

We should observe men in the process of answering that critical and ubiquitous question—"what matters most now?" And we should thus observe valuation in action

And here we should find that the alternatives which these men were comparing with each other were by no means so simple or so stable as they appeared No issue ever is or ever ought to be decided "on its merits", if that is taken to mean "without reference to its repercussions on other issues which its decision will affect" The views people take of an issue depend on how they "see" it It can be seen as part of many different questions, people will see it as part of those questions which most concern themselves They cannot be proved wrong, they can all be proved right So what? Does valuation dissolve in discrimination, and is discrimination simply a matter of what you fancy?

Perhaps research would throw some light on these questions They are important and they are real One thing I am sure it would tell us The way we see the question depends very much on the kind of question we are accustomed to deal with Our society is run by people who are accustomed and professionally trained to see and answer technological questions and financial questions and legal questions and administrative questions Only very few people are accustomed and professionally trained to see and answer human questions about people as people We may be thankful that their number is increasing, for this imbalance cannot fail to distort the goals of public health But this alone is, I think, a very small part of the answer

I have suggested a few of the many ways in which we can hope to deepen our knowledge of ourselves and of the processes of which we are part—of all fields of knowledge the most intractable and the most important I believe that this knowledge will never equal the other sciences in giving us the power to predict, but that it can none the less promise something different and far more important—a greater power to understand And it is this which in the end will determine how much and how wisely we can contribute to the seeking of our own health Tyrants may shout orders, within us and without, but the voice we obey in the end speaks very quietly in the indicative mood

BASAL METABOLIC RATE IN THYROTOXICOSIS

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The usual standards for the normal basal metabolic rate (B M R) in clinical work are those of Aub and Du Bois (1917) Robertson and Reid (1952) showed that these are inapplicable in this country, and provided alternative standards, which are not yet, however, widely used The present study, in which the two reference standards have been compared in the diagnosis of thyrotoxicosis, suggests that these new standards should be generally adopted Many workers have commented on those thyrotoxic patients whose B M R s lie within the normal range, and a special study has been made of this group

Materials and Methods

The B M R was estimated in 209 people by the same experienced technician using a Benedict-Roth apparatus All were admitted to hospital and were given 200 mg of butobarbitone twelve hours before each test The estimations were done in duplicate on two successive days and the lowest of the four values was accepted The results were expressed as the percentage deviations from the normal means in terms of Robertson and Reid and Aub and Du Bois standards

In 116 cases (35 non-toxic, 81 toxic) the diagnosis was definite on clinical grounds and confirmed by radio-iodine studies In 93 cases (38 non-toxic, 55 toxic) the diagnosis was classified as doubtful, the criterion for inclusion in this group being that diagnostic doubt had been present in the mind of at least one hospital physician to such a degree that he considered radio-iodine studies were necessary to establish the diagnosis All cases in this group, which is termed "initially doubtful" in table I, were assessed clinically in the conventional manner and also by the application of statistical discriminant analysis to the clinical features of each case, as described by Crooks, Murray, and Wayne (1957) Radio-iodine studies, consisting of the four-hour uptake of radio-iodine and the forty-eight-hour plasma protein-bound radioactivity, were carried out in each case in addition to the B M R estimation On the basis of all the available evidence a provisional diagnosis was reached In all cases where diagnostic doubt remained after full investigation, a therapeutic trial with an anti-thyroid drug was carried out. In the "doubtful" group

TABLE I—ACCURACY OF DIAGNOSIS

Initial diagnosis	Final diagnosis	No of cases	Diagnosis correct by			
			Robertson and Reid	Aub and Du Bois		
				+10%	+15%	+20%
Definite	Toxic	81	79 (98%)	75 (93%)	68 (84%)	58 (72%)
	Non toxic	35	31 (89%)	33 (94%)	33 (94%)	34 (96%)
	Total	116	110 (95%)	108 (93%)	101 (87%)	92 (79%)
Doubtful	Toxic	55	41 (75%)	29 (53%)	21 (38%)	14 (25%)
	Non toxic	38	33 (87%)	36 (95%)	38 (100%)	38 (100 %)
	Total	93	74 (80%)	65 (70%)	59 (63%)	52 (56%)

TABLE II—10 THYROTOXIC PATIENTS WITH B.M.R. WITHIN THE NORMAL RANGE (ROBERTSON AND REID) RATE BEFORE AND AFTER THERAPY

Patient no.	Weight (compared with average for height and age)	Therapy		B M R. (%) (Robertson and Reid)	
		Type	Euthyroid after	Before treatment	After treatment
1	−16%	Radio-iodine	20 weeks	−11	−24
2	−22%	”	20 ”	−4	−7
3	−28%	”	12 ”	+14	−10
4	−16%	”	16 ”	−8	−5
5	−10%	Methyl thiouracil	8 ”	−14	−6
6	−3%	”	12 ”	−8	−6
7	−4%	Potassium perchlorate	24 ”	−3	−7
8	−3%	”	16 ”	+12	−13
9	−13%	”	8 ”	−13	−12
10	−2%	”	6 ”	−15	−5

the final diagnosis was established only after the results of therapy were known

10 patients with B.M.R.s within the normal range, but in whom all other evidence pointed to thyrotoxicosis, were given anti-thyroid therapy as shown in table II Patients 1, 2, 3, and 4, who received radio-iodine therapy, were assessed clinically each month, and when they were euthyroid the B M R was repeated In the remaining patients, who received anti-thyroid drugs, the B M R was estimated at fortnightly intervals until they were clinically euthyroid

Results

The results in the 209 subjects are shown in table I It is clear that, in patients in whom there was never any clinical doubt, the Robertson and Reid standards (95% correct diagnoses in 116 cases) possess no advantages over the Aub and Du Bois standards, taking the upper limit of normal of the latter as +10% (93% correct diagnoses in the same cases) The comparable figures, using +15% and −20% as the upper limits (Aub and Du Bois), were 87% and 79% respectively

The greater value of the Robertson and Reid standards is apparent in the results in the group in which there was diagnostic difficulty (table I) 80% of 93 such cases were correctly diagnosed by B M R. estimations using the Robertson and Reid standards, compared with 70% using Aub and Du Bois standards, taking the upper limit of normal of the latter as +10% The latter standards became progressively less useful when higher upper limits (−15% and +20%) were used The greatest discrepancy between the two standards was in the group that contained initially doubtful cases finally shown to be toxic Three-quarters of these were correctly diagnosed by B.M R estimations according to the Robertson and Reid standards, while only a half (upper limit +10%), or a quarter (upper limit +20%) were correctly diagnosed when the Aub and Du Bois standards were used

Of 10 toxic patients whose B M R s lay within the normal range—the mean value was +10 2% (Robertson and Reid)—the B M R. fell in all after treatment to a mean value of −8 3% This reduction in the B M.R. is illustrated in the figure Patient no 1 (−24%) was the only one whose B M R. fell below the lower limit of the normal range (Robertson and Reid) Neither this patient nor any of the others had clinical or laboratory evidence of hypothyroidism

Discussion

Over many years, estimation of the basal metabolic rate has been a standard method of assessing thyroid function With the advent of more recent diagnostic procedures, such as radio-iodine tests, its usefulness has been questioned There are, however, some occasions when radio-iodine tests may be unreliable—for example, after the use of anti-thyroid drugs (Foote et al 1952), operations (Silver et al 1955), or radio-iodine therapy (Ansell et al 1951) In such circumstances B M R estimations have their greatest value

The conflicting opinions about the usefulness of the test arise from variations in technique, in selection of cases, and in standards used

Variations in Technique

Using a less satisfactory technique than in the present series and applying the Aub and Du Bois standards, Goodwin et al (1951) showed that there was a poor correlation between the results of B M R estimations and the final diagnoses in a series of cases of suspected thyrotoxicosis On this basis the defects of the B M R as a diagnostic procedure were emphasised by Wayne (195[illegible]

The technique used to determine B M R in the present series is a compromise between that of Robertson (19[illegible] and Boothby et al (1936)

Robertson advocated repeated estimations until the second of two duplicate readings differed by no more than 5% from the first duplicate on the same day Boothby et al, on the other hand, to eliminate the effect of training, took as their basal level the first determination They argued that it is [illegible] practicable to obtain true B M R s in clinical practice We agree with this opinion, but also with the criticism of Roo[illegible] (1944) that nervous tension is not uncommon at the [illegible] test, particularly in thyrotoxicosis, and that initial readings are commonly higher than later readings

The technique we have described meets in part those [illegible] tions while remaining a practical diagnostic procedure [illegible] confusion could have been avoided if the term "[illegible] metabolic rate" had been substituted in the past for "[illegible] metabolic rate" as suggested by Boothby et al (193[illegible]

Selection of Cases

It should be noted that 9 of 73 non-toxic su[illegible] raised B M R s according to the Robertson [illegible] standards This is in striking contrast to the [illegible] Keating et al (1950) who found that only 49% [illegible] euthyroid patients had B M R s within their n[illegible] of ±13% (Aub and Du Bois) This discrepan[illegible] the use of the different standards plays no [illegible] from their deliberate inclusion of a number of [illegible] patients with diseases in which the B M R [illegible] outside normal limits This illustrates the pr[illegible] which varying selection of cases can ha[illegible] workers' results Another example of the [illegible] tion of cases is the varying proportion of [illegible] doubtful cases of hyperthyroidism in differen[illegible] is shown in table I, where a diagnostic [illegible] moderate for frankly toxic cases falls to 75% [illegible] ns done presenting diagnostic difficulty are co[illegible] hrship are presented in their present form [illegible] ly propor- this fallacy [illegible] from the

Reference Standards

[illegible] The thyroid [illegible] excessively

The most important factor [illegible] st or present ment concerning the [illegible] X rays of the estimations is the use of [illegible] asma protein-

In an admirable review [illegible] in the accepted points out that in various [illegible] um-l-thyroxine have been −10%, +12% [illegible] d after 2 months the mean standards laid

As a result of obs[illegible] e 1 His deafness thyrotoxicosis before (1952) concluded that too high for this country because of either population differences or differences in technique, or a combination of both Accordingly they produced new standards for the basal metabolism of normal people in Britain based on a study of 987 males and 1323 females aged between 3 and 80 years Their normal ranges for age and sex were calculated on the basis of ±2 S D from the mean values (about ±15%) Each case in our series has been assessed on the basis of these normal ranges An estimate of B M R expressed in terms of these standards will be about 10% higher than an estimate based on those of Aub and Du Bois

Accuracy of Diagnosis

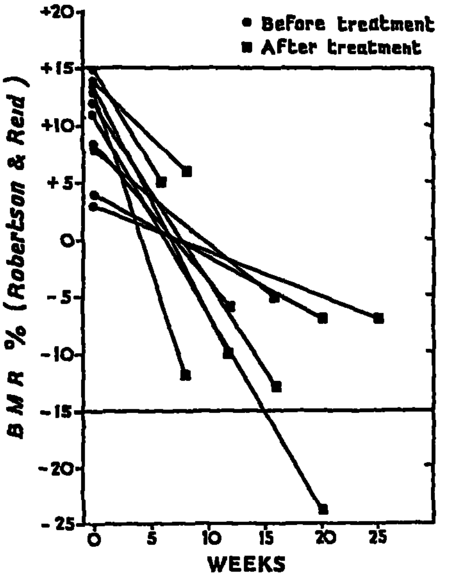
The use of the British standards in the present series has produced an improvement in the diagnostic accuracy of the B M R estimation in cases of clinical diagnostic difficulty This is best seen in the cases of this group finally shown to be toxic, where the diagnosis was correct in 41 of 55 subjects when Robertson and Reid standards were used, but in only 29 of 55 when the lowest percentage deviation (+10%) from the mean Aub and Du Bois standards was used It must be admitted, however, that the standards of Robertson and Reid possess no diagnostic advantage over those of Aub and Du Bois when the non-toxic cases of the important "doubtful group" are considered Use of the Aub and Du Bois standards (+10%) led to a correct diagnosis in 36 of the 38 cases, in which Robertson and Reid standards led to correct diagnosis in only 33 It is generally accepted that technical errors in B M R estimations tend to produce results which are falsely high

Such errors are most likely to result in misdiagnosis when very nervous patients, wrongly suspected of thyrotoxicosis, are being tested These circumstances would operate in favour of the Aub and Du Bois standards in diagnosing non-toxicity, since estimations of B M R based on these standards are 10% lower than those based on the Robertson and Reid standards The slight advantage of the Aub and Du Bois standards in the diagnosis of non-toxicity in the present series can be explained on this basis, but does not compensate for their deficiencies in diagnostic accuracy when subjects are toxic In the latter, especially in mild cases, the Aub and Du Bois standards, since they are higher, will produce a greater number of B M R s within the normal range The elimination of technical errors in estimations, while increasing this tendency, is to the advantage of the Robertson and Reid standards

For example, Fraser and Nordin (1955) found that "sleeping metabolic rates" of nervous people fell within the normal ranges of the Robertson and Reid standards, though their metabolic rates while awake were above these ranges The "sleeping metabolic rates" of their thyrotoxic patients did not fall below the upper limit of normal (Robertson and Reid) but some would have been normal if the Aub and Du Bois standards had been used

It is felt, however, that the advantages of their procedure over that described in the present study are not commensurate with the labour involved and the inconvenience to the patient In the same way the adoption of the open-circuit method of estimating the B M R (Fowler et al 1957), as advocated by Keating (1957), would, by diminishing the effect of technical errors, increase the number of normal cases falling within the normal limits of the Robertson and Reid standards

An objection to the diagnostic use of B M R estimations is the occurrence of "extrathyroidal-hypermetabolism" In our experience such states do not in practice give rise to diagnostic difficulty, since they are readily recognised to luded On the other hand, hyperthyroidism can



Changes in B.M R following therapy in 10 thyrotoxic patients with initially "normal" B M R s

exist in association with a "normal" B M R, as can be seen from the results of the present series, in which 16 of 136 toxic patients had B M R s in the normal range (Robertson and Reid) As Means (1937) pointed out, this may happen when the patient's B M R in health lies at the lower limit of the normal range. This opinion was also held by Bartel (1950), who reported that 8% of 1000 hyperthyroid patients had B M R s less than +20% (Aub and Du Bois), and that following partial thyroidectomy some of these cases had a low B M R without evidence of hypothyroidism This explanation gains further support from the changes in B M R following therapy (figure and table II) in 10 cases of the present series, in all of which a normal B M R was associated with undoubted thyrotoxicosis When these patients became euthyroid, their B M R s in health were at the lower limits of the normal range

An alternative reason for this association may be considered in patient no 5, who, though thyrotoxic, was 10% above her average weight for age and height, and in patients 6, 7, 8, and 10, who had weights closely approximating to the average As long ago as 1922, Boothby and Sandiford suggested that heat-production is proportional to the active protoplasmic mass of the body, and that this in turn is related to surface area In view of the fact that depot fat has a very low rate of oxygen utilisation (Krebs and Johnson 1948), increase in fat will result in an increase in surface area without a proportionate change in basal oxygen consumption This effect of depot fat on the B M R as calculated from surface area has also been recognised by Keys and Brozek (1953) and Bernstein et al (1956) It is possible, therefore, that in the above 5 patients who gave a history of weight-loss, but were previously obese, much excess adipose tissue still remained at the time of the B M R estimations The finding, therefore, of a "normal" B M R in a patient in whom there are grounds for suspecting thyrotoxicosis should not preclude the diagnosis, especially if the weight approximates to the average for height and age when there is a history of weight-loss The changes in the B M R following therapy are of diagnostic value in such cases, as suggested by Robertson (1934) These patients should not be confused with the "plump thyrotoxic" patients, described by Trotter and Eden (1941), who had high B M R s but gave a previous history of weight-increase and lost weight following anti-thyroid therapy

Summary

Estimations of basal metabolic rate, applying both Robertson and Reid and Aub and Du Bois standards have been carried out in 209 subjects to assess thyroid function In the diagnosis of suspected thyrotoxicosis the use of Robertson and Reid standards increased the accuracy of the test By these standards 10 patients with thyrotoxicosis had "normal" B M R s which fell following anti-thyroid therapy In some cases this association may be due to the occurrence of the disease in patients whose B.M R s in health are much lower than the established mean values In others it may be due to the presence of excess adipose tissue influencing the calculation of surface area without a parallel effect on oxygen consumption

We should like to acknowledge the technical assistance of Miss S R Willis

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ASSOCIATION OF CONGENITAL DEAFNESS WITH GOITRE

THE NATURE OF THE THYROID DEFECT

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Russell Brain (1927) described five families, all living in the eastern part of Greater London, of which one or more members were deaf from birth and had goitres which appeared to date from childhood All the affected persons had both goitre and deafness but were well developed physically and of normal intelligence In all five families only one generation was affected Brain suggested that in these families both goitre and deafness were caused by one or more recessive genes This rather remarkable association of goitre and deafness does not seem to have been commented on by other authors until the recent communications of Deraemacker (1956) from Belgium and of Thieme (1957) from Michigan These described single families resembling those recorded by Brain in that the affected members had both goitre and deafness and were well developed physically and mentally, and only one generation was affected It appears that either the association has been often observed but dismissed as fortuitous, or that something like a minor epidemic of deafness and goitre occurred in East London in the 1920s

NUMBERS OF AFFECTED AND UNAFFECTED SIBS WITH THEIR SEX DISTRIBUTION IN ALL FAMILIES DESCRIBED

Families	Affected sibs		Unaffected sibs	
	Male	Female	Male	Female
Poplar (Brain 1927)	2	1	0	0
Plaistow (Brain 1927)	1	2	2	1
Sheerness (Brain 1927)	2*	1	0	0
Bethnal Green 1 (Brain 1927)	0	2	3	1
Bethnal Green 2 (Brain 1927)	1	0	0	4*
Deraemacker's (1956) family	3	0	5	4
Thieme's (1957) family	2	1	1	2
Present family	1	1	0	0
Total	12	8	11	12

* The sex of one member of each of these subgroups is not clear in the text.

In the recorded families (see table) the goitre and deafness were roughly equally distributed between the sexes Other types of goitre are commoner in females than in males, so it seems likely that there is some specific inherited defect of thyroid function which could explain the unusual sex-distribution in these families With this in mind we have investigated thyroid function in two sibs who appear to have the syndrome described by Brain

Case-reports

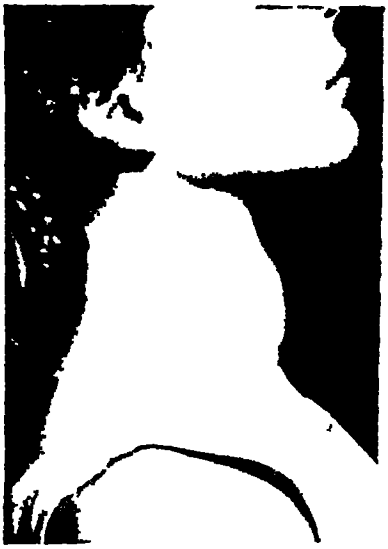

Fig 1—Case 1, showing goitre

Case 1—A girl, aged 12, was referred to us from the pediatric department of the South London Hospital for Women and Children She had always lived in South London Her deafness was first noticed at the age of $2^1/_2$ years and the thyroid swelling at 8 She was a full-term baby, her mother being well throughout pregnancy Delivery was normal She was breast-fed for 8 weeks and then weaned to cow's milk She developed normally, apart from a speech defect related to her deafness She walked at 9 months, and her dentition started at 8 months and was complete at 2 years At the age of 3 years she was diagnosed at the Royal National Throat, Nose and Ear Hospital as having congenital nerve-deafness of moderate degree She had had no serious illness She has done extremely well at school, having recently won a scholarship

She was an alert well-grown girl with normal body proportions There were no obvious deformities apart from the thyroid swelling, which was considerable (fig 1) The thyroid was thought to be nodular on palpation but was not excessively vascular There was no clinical evidence of past or present hypothyroidism This was confirmed by normal X rays of the pituitary fossa and femoral heads, and by a plasma protein-bound iodine level of 5 9 µg per 100 ml (within the accepted normal range) After all the investigations sodium-l-thyroxine 0 2 mg was administered daily to this girl, and after 2 months the gland became smaller

Case 2.—A boy, aged 9 was brother to case 1 His deafness was noticed at the age of 2 years No thyroid swelling had been noticed by the mother He was born at full term of a normal pregnancy He was breast-fed until weaned at 8 months He walked at 11 months, and his dentition began at 7 months and was complete at 2 years He was seen at the age of 2 years at the Royal National Throat, Nose and Ear Hospital, where a diagnosis of familial congenital nerve-deafness was made His deafness was greater than his sister's He had had no serious illness

He was an intelligent well-grown boy with normal body proportions His goitre was just visible and very soft There was no vascular bruit There was no clinical or X-ray evidence of hypothyroidism The plasma protein-bound iodine was also normal (4 3 µg per 100 ml) This boy was also given sodium-l-thyroxine 0 2 mg daily on the completion of investigations

Family history —The mother and father were well and had no goitre or deafness This was confirmed by examination in the case of the mother The parents were not related There were no other children There is no history of goitre or deafness on either side of the family

Investigations with Radioiodine

These investigations were limited by consideration of radiation effects to a single small dose of ^{131}I for each child and a perchlorate test using the short half-life isotope ^{132}I

Cases 1 and 2 and their mother were each given ^{132}I 20–40 µC by mouth about 5 hours after a meal Counts were made simultaneously over the thyroid and thigh with a Geiger counter 50 and 60 minutes after the dose Immediately after the 60-minute count the two children drank a solution containing 200 mg of potassium perchlorate in 25 ml of water The mother drank a solution containing 400 mg of potassium perchlorate in 50 ml of water The counting-rates opposite the neck and the thigh were measured at 10, 20, 30, 40, and 50 minutes after the administration of potassium perchlorate The same technique has been used previously in the investigation of other types of goitre (Morgans and Trotter 1955, 1957) Fig 2 shows a discharge of radioactivity from the thyroid gland in both case 1 and case 2 after the drink of potassium perchlorate The fall in the neck counting-rate was accompanied by a rising thigh count as the labelled iodine atoms passed from the thyroid into the iodide space The mother showed no such changes, her response being typical of the usual behaviour of a person with a normally functioning thyroid

On another occasion both case 1 and case 2 were given a tracer dose of about 5 µC of ^{131}I, and counts were made over the thyroid with a wide-aperture scintillation counter at varying intervals up to 4 days after the dose Case 1 showed a high 24-hour uptake (67% of the dose), whereas that in case 2 was at the upper limit of normal (51%) Case 1 showed a fairly rapid fall in the counting-rate over the thyroid (3% daily from the 2nd to the 5th day), whereas the fall in case 2 was 0 8% daily (in our experience the normal rate of fall is less than 2% daily)

Discussion

In all respects the family described here appears to fall into the same group of cases as those described by Brain (1927), Deraemaeker (1956), and Thieme (1957) only one generation seems to be affected, the deafness is congenital, the goitre appears later in childhood, and there is no evidence of hypothyroidism at any time The accompanying table shows the sex and number of affected and unaffected sibs in all the families we have been able to trace, including our own The observed distribution is probably compatible with the effects of a single recessive gene The proportion of affected sibs appears larger than would be expected on this hypothesis, but this can probably be accounted for by the unavoidable selection of affected families Families in which only one of several sibs had the combination of congenital deafness and would be unlikely to be described as examples of this syndrome Although it is possible that other families may be found in which goitre and deafness are in some cases dissociated, it is rather striking that in all the families known at present neither condition has occurred by itself in any member

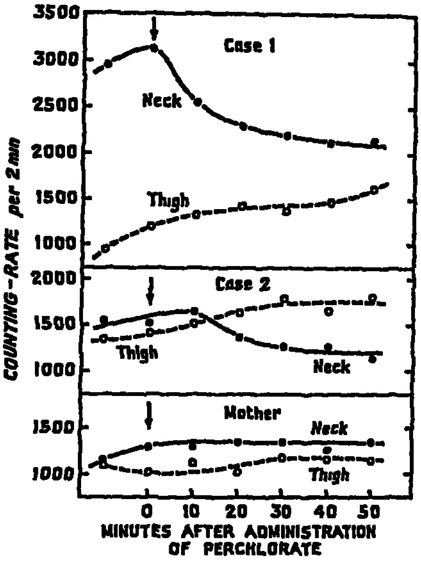

Fig 2—Counting-rate over neck and thigh in the two patients and in their normal mother Potassium perchlorate was administered at 0 minutes on the time-scale used in these graphs *This corresponds to 60 minutes after* the administration of ^{132}I

The only other study of thyroid function in this condition of which we are aware is by Thieme (1957) In one of his affected sibs the 24-hour uptake of radioiodine was normal Measurements of overall uptake may, however, not reveal a partial defect in hormone synthesis when this has been compensated for by pituitary overactivity Thus the total uptake of radioiodine may be normal or above normal in Hashimoto's thyroiditis (Doniach et al 1957), yet testing with perchlorate reveals a defect in organic binding of iodine (Morgans and Trotter 1957) A similar situation may be postulated in the present two cases The administration of perchlorate (or of thiocyanate) causes any radioiodine which may be present as iodide to be discharged from the thyroid (Stanley and Astwood 1948, Stanbury and Wyngaarden 1952), the occurrence of such a discharge is shown by a simultaneous fall in the neck count and a rise in thigh count, as in the present two cases

When perchlorate is given to a person with a normally functioning thyroid an hour after a tracer dose of radioiodine, this discharge is not seen, the rise in the neck count is arrested, but the counting-rate does not fall, as is illustrated by the behaviour of the mother of the present patients (fig 2) When total inability to bind iodine is present, as in the goitrous cretins described by Stanbury and Hedge (1950), all radioiodine in the thyroid is present as iodide and is dischargeable by perchlorate or by thiocyanate at any time after the administration of the radioiodine Partial defects of the same type can be demonstrated only by giving perchlorate an hour or so after the radioiodine, and may reasonably be regarded as showing a slowing down in the rate of iodine-binding When an active goitre is present, the large mass of thyroid tissue can bind a normal or greater than normal proportion of radioiodine within 24 hours, even though the rate of binding is subnormal In case 1 the rapid rate of loss of ^{131}I from the thyroid in the second test may have indicated excessive stimulation by thyrotrophic hormone

We report these two cases as examples of a syndrome, of both genetic and biochemical interest, which might well repay further study if more cases come to light

From the practical point of view it is very probable that thyroid medication begun in early childhood will obviate the need for thyroidectomy This operation had to be performed in most of the published cases of this syndrome by the time they were recognised There is no reason to suppose that thyroid medication will have any effect on the deafness

Summary

Two siblings are described in whom nerve-deafness, present from birth, was associated with a goitre developing during childhood The children were euthyroid and had developed normally in other respects

A review of the literature shows that this syndrome has usually been observed in two or more sibs but not in their parents In the affected families neither congenital deafness nor goitre has occurred singly

In the published cases the numbers of males and females affected has been about equal This contrasts with the usual preponderance of females among cases of goitre, and suggests an uncommon type of thyroid defect

Studies with radioiodine in the present two cases showed that, although the 24-hour uptake was high, some of the radioiodine present in the thyroid an hour after the tracer dose was dischargeable by perchlorate This finding suggests a partial defect in the organic binding of iodine, perhaps compensated for by increased thyrotrophic secretion.

Our thanks are due to Dr Mary Wilmers for bringing the cases to our notice, to Mr J C Ballantyne for the audiometric investigations, to Mrs K Rodgers (working in Prof H A Krebs' laboratory at Oxford) for estimating the protein-bound iodine, to Dr J B Stanbury for drawing our attention to Dr Thieme's work, and to Dr Thieme for allowing us to see his manuscript before publication

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NEW METHOD OF PHENOBARBITONE ADMINISTRATION IN THE TREATMENT OF EPILEPSY

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Charles Locock's introduction of bromides in the treatment of epilepsy achieved good results, though the mechanism of action was and still is obscure With the use by Hauptmann (1912) of phenobarbitone came the first real advance in specific anticonvulsant therapy

Keller and Fulton (1931) showed that specific corticomotor depression was produced by phenobarbitone Merritt and Putnam (1938) brought forward further evidence of its anticonvulsant properties, both in animals and in psychiatric patients undergoing chemical and electric shock therapy Barany and Stein-Jensen (1946) and Brown et al (1953) showed that phenobarbitone is one of the most potent anticonvulsants available, with a broad spectrum of activity

Other drugs since introduced, particularly for petit mal, are not completely satisfactory because of their side-reactions and toxicity The overall value of phenobarbitone in the treatment of epilepsy is well summarised by Garland (1957)

> "The barbiturates are the least toxic of all the anticonvulsant drugs and are still the first choice in the treatment of major, temporal lobe and other focal seizures The hydantoins and primidone, alone or in combination, may succeed when the barbiturates have failed but they produce toxic reactions, though these are not usually serious if recognized early Finally, it would seem that hæmatological changes of major or minor import are probably much commoner than has yet been suspected when using any of the modern anti-convulsants"

The major effects of the barbiturates, and of phenobarbitone in particular, are increased recovery-time and increased threshold for cerebral neurones in general Phenobarbitone has also a selective anticonvulsant effect, unrelated to the depressive and sedative qualities, no other barbiturate, except methylphenobarbitone and metharbital ('Gemonil'), has this effect. The cerebral cortex and the reticular system seem to be the most sensitive parts of the brain to barbiturate effects

Preparations of phenobarbitone now in common use are not completely successful, they do not always abolish fits entirely and often cause toxic effects It seemed to me likely that changing blood-levels of the drug might explain this, toxic effects being caused when the level was high and fits appearing when it was low It seemed logical to try a preparation which releases phenobarbitone slowly over a long period and might be expected to produce a more constant blood-level I now report results in epileptic patients in whose treatment phenobarbitone 'Spansules' (Smith, Kline & French Laboratories) were substituted for the same drug taken in tablet or solution form Each spansule contains phenobarbitone gr $1^1/_2$ in coated granules, which release the drug at a uniform rate, ensuring a slow steady absorption over a long period

Methods and Material

18 psychotic, epileptic men were studied They had had convulsions and psychoses for more than ten years I examined them every four months as inpatients, and followed them up throughout 1955, 1956, and 1957—except for 1 (case 14) who was not admitted until June, 1955 The same nurses attended the patients, and the same scheme of interpreting and recording the convulsions was followed over the three years Most of the patients have been treated and cared for in the same ward for at least the past four years The form of epilepsy was classified as general paralysis with major and minor convulsions in 1, post-traumatic jacksonian in 1, idiopathic petit mal in 2, post-traumatic grand mal in 1, and idiopathic grand mal in 13, with hysterical overlay in 1 and periods of status epilepticus in 1

These cases were not particularly selected, but most probably had the severest form of epilepsy, both in the psychosis and in the frequency and severity of convulsions

All patients were fully investigated, by means of frequent blood and urine studies, chest and skull radiographs where necessary, and complete physical and neurological examination, with particular attention to tests of speech, walking, and muscular coordination and balance Because of the mental difficulties and general uncooperative attitude of most of the patients, few electroencephalograms could be made

All the patients, except cases 8, 9, 13, 16, and 17, were receiving phenobarbitone solution or tablets in total daily doses of gr $1–4^1/_2$, the 5 exceptions were receiving primidone only Cases 1, 4, 5, and 14 were given primidone as well as phenobarbitone, the dose of primidone was

TABLE I—TOTAL NO OF EPILEPTIC CONVULSIONS DURING THE INVESTIGATION

Year	Jan	Feb	March	April	May	June	6 mos total	July	Aug	Sept	Oct	Nov	Dec	6 mos total	12 mos total
1955															
Day	24	25	15	18	22	28	132	27	32	18	34	22	37	170	302
Night	48	32	50	38	40	45	253	28	39	40	41	37	59	244	497
1956															
Day	31	37	23	19	22	21	153	19	11	6	14	10	6	66	219
Night	48	48	37	32	29	29	223	15	15	15	11	10	7	73	296
1957															
Day	12	7	5	5	5	2	36	—	2	—	1	—	—	3	39
Night	11	14	8	3	3	—	39	1	2	—	1	—	—	4	43

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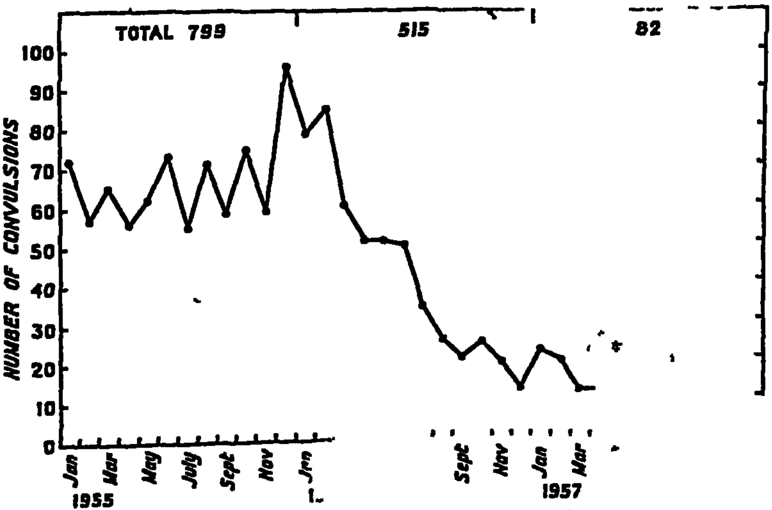

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1955															
Day	24	25	15	18	22	28	132	27	32	18	34	22	37	170	302
Night	48	32	50	38	40	45	253	28	39	40	41	37	59	244	497
1956															
Day	31	37	23	19	22	21	153	19	11	6	14	10	6	66	219
Night	48	48	37	32	29	29	223	15	15	15	11	10	7	73	296
1957															
Day	12	7	5	5	5	2	36	—	2	—	1	—	—	3	39
Night	11	14	8	3	3	—	39	1	2	—	1	—	—	4	43

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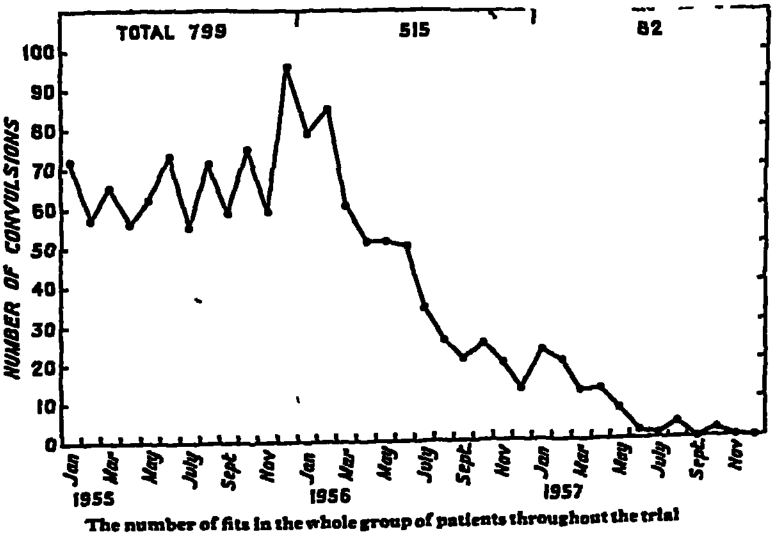

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TABLE II—DATA ON 18 CASES OF EPILEPSY

Case no	Age (yr)	Diagnosis	Results of treatment					
			No of convulsions				Personality	
			1955	1957			1955	1957 Improvement
				Total	Jan -June	July-Dec		
1	33	Traumatic jacksonian unsuccessful operation	82	0	0	0	Violent	Striking
2	39	Idiopathic grand mal	48	12	11	1	Violent	Moderate
3	37	Idiopathic grand mal	66	4	4	0	Retarded	Striking
4	47	General paralysis with major and minor convulsions	25	4	4	0	Retarded	Slight
5	32	Idiopathic grand mal	32	3	3	0	Violent	Striking
6	37	Idiopathic grand mal	91	7	7	0	Retarded	Striking
7	48	Idiopathic grand mal	48	4	4	0	Violent	Moderate
8	43	Idiopathic grand mal	28	3	3	0	Retarded	None
9	54	Idiopathic grand mal	17	1	1	0	Retarded	Striking
10	48	Idiopathic grand mal	15	9	6	3	Violent and retarded	Striking
11	36	Idiopathic grand mal with hysterical overlay	30	10	8	2	Retarded	Striking
12	48	Post-traumatic grand mal	67	0	0	0	Violent	Striking
13	52	Idiopathic petit mal	53	2	2	0	Retarded	Moderate
14	24	Idiopathic grand mal, episodes of status epilepticus	57	1	0	1	Violent	Striking
15	55	Idiopathic petit mal	49	6	6	0	Retarded	Striking
16	64	Idiopathic grand mal	3	0	0	0	Retarded	Slight
17	55	Idiopathic grand mal	10	2	2	0	Retarded	Striking
18	45	Idiopathic grand mal	78	14	14	0	Retarded	Striking

symptoms were probably attributable to toxicity in most cases, but in some they were present when only primidone was being given, and were abolished during phenobarbitone spansule treatment though primidone was still being given in the same dose

The blood-barbiturate content was estimated in 3 cases while spansules were being given Samples were taken twice in a twenty-four-hour period, the first an hour and a half after the last medication at night, and the second next morning while the patient was fasting and had not yet received his medication, there was thus some twelve hours' interval between the collection of specimens, during which no phenobarbitone was given The levels were found to be

Case	*Specimen*	*Blood-barbiturate (mg per 100 ml)*
6	First	5 66
	Second	6 04
11	First	5 89
	Second	5 31
18	First	4 66
	Second	5 18

These levels are much higher than those that a non-epileptic person would be expected to tolerate without either unconsciousness or ataxia, or both There was little variation between the two readings in any of the cases

Discussion

Early in this study it became evident that the spansule phenobarbitone was producing the type of result hoped for but rarely experienced I expected at least slight toxicity in the early stages, but observed none

The lack of toxicity might be attributed to the fact that most of these patients had been receiving phenobarbitone for many years, and had developed tolerance, either partial or complete, from repeated administration of the drug, but before spansules were used signs of toxicity were seen—both mental (sluggishness, slowness of speech and comprehension, quarrelsomeness, irritability, hostility, paranoia, and clouding of consciousness) and physical (thickness and slurring of speech, ataxia, and mild rashes) The blood-picture and the patients' appetites were normal throughout the entire period

One of the main reasons for the good results, and their maintenance and constancy, and for the low toxicity, seems to be that the change in the blood-barbiturate is small

A future report will give further details of blood-barbiturate levels and electroencephalographic studies

Summary

In 18 psychotic epileptic patients, 'Spansule' phenobarbitone (a preparation which allows even absorption and steady blood-levels) was substituted for phenobarbitone in solution or tablet form, or added where primidone had been the only treatment

The incidence of convulsions was very strikingly reduced In the first six months of the study, before the introduction of spansules, the group had a total of 385 convulsions, in the last six months the total was 7 The personality and mental state improved in most cases, and toxicity was much reduced

The good effects and low toxicity are attributed to the constancy of the blood-barbiturate level that was attained

I am very grateful to Sir Geoffrey Nightingale, physician-superintendent of Warley Hospital, for help and cooperation in this study, to Sir Francis Walshe, F R S, for advice and criticism, to Mr John V Crawford, F R C S, and Dr T J Wright, of the London Hospital, for valuable assistance, and to Mr A W Pettit of the pathology department, Mr H W Layer of the pharmacy, and the male nurses of Warley Hospital

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TRANQUILLISERS AND PATIENTS' ENVIRONMENT *

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SENIOR REGISTRAR, CANE HILL HOSPITAL, COULSDON, SURREY

There is good reason to think that tranquillising drugs are now being used too often and in excess (Sargant 1956, *British Medical Journal* 1957, World Health Organisation 1957) This paper describes an attempt, in two chronic "refractory" wards of a mental hospital, to obtain equal tranquillity by a different means—namely, improvement of the patient's environment The therapeutic effect of a good environment has been frequently demonstrated (Schwartz and Stanton 1950, Tudor 1952, Walk 1954, Carstairs et al 1955, Bickford 1955, Greenblatt and Brown 1955, May 1957, Miller 1957), and I

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* Summary of a paper read to the Surrey Inter-hospitals Psychiatric Association, Sept 12, 1957

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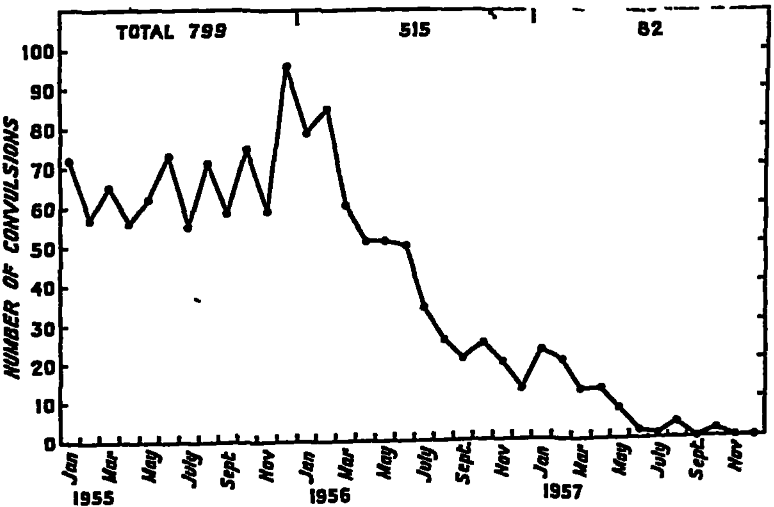

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The greater improvement in ward A than in ward B during period IV was probably due to the support of the staff in ward A, for no other new factor was introduced in either ward Improvement was maintained in both wards while placebos were being given, and disturbances increased after the withdrawal of placebos in ward A This suggests that placebos have some therapeutic value It may be that the initial improvement gives both the staff and the patient confidence in the drug This may explain why placebos can maintain improvement, while their withdrawal leads to deterioration This confidence may also be responsible, to some extent at least, for the belief that long-continued use of these drugs is necessary to maintain improvement Our results suggest the possibility that these drugs may sometimes be used unnecessarily, exposing the patients to possible toxic effects and the hospital to unnecessary expense

Thanks are due to Dr A Walk, physician-superintendent, of the hospital, and to Dr J T Hutchinson for their interest and helpful criticism, and to the nurses and occupational therapists for their cooperation

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ARTIFICIAL RESPIRATION WITH THE TUNNICLIFFE BREATHING-JACKET

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THE cuirass respirator has been in general use for many years and has proved its worth as a convenient source of artificial respiration in the partially paralysed patient Unfortunately, however, it restricts the expansion of the thoracic cage during inspiration, with the result that the maximum ventilation it can provide is much less than can be obtained in those methods of artificial respiration in which the chest is left free—namely, the tank respirator and intermittent positive-pressure respiration (I P P R) The cuirass is, moreover, liable to make the chest wall sore if used continuously For these reasons, though it has occasionally been used in the treatment of acute cases of poliomyelitis (Lindahl and Strom 1957), its principal importance lies in the treatment of convalescent patients who can breathe spontaneously for several hours daily (Kelleher et al 1952)

The Tunnicliffe breathing-jacket,* which we describe here, in some ways resembles the cuirass respirator, but it is designed to avoid restricting the movement of the thoracic cage or of the abdominal wall It is an important innovation, and we are able to report some observations demonstrating that increased ventilatory efficiency is obtainable with it

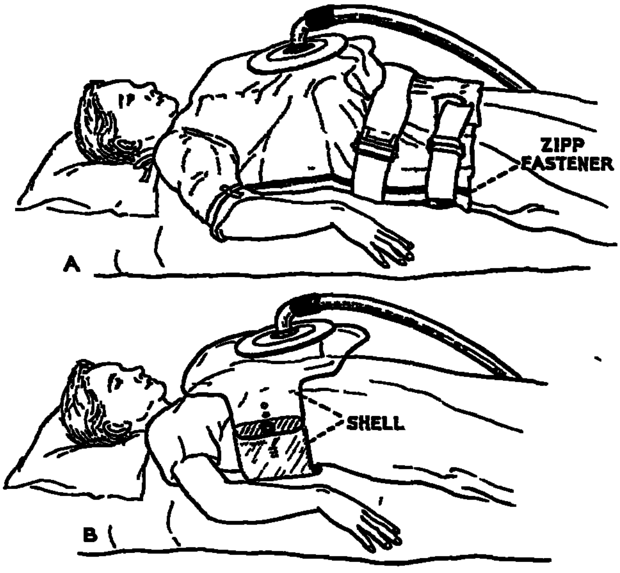

Fig 1—Tunnicliffe breathing-jacket A The jacket in use B The plastic shell which holds it clear of trunk

Description

Jacket

The jacket is made of cotton and nylon cloth, and the seams have been reduced to a minimum A 'Zipp' fastener runs from behind the right greater trochanter, up the flank, and behind the right shoulder to the side of the neck The jacket has short sleeves and at its lower margin reaches below the buttocks (fig 1, A) A plastic shell passes round the chest, holding the jacket away from the trunk (fig 1, B)

When the pressure in the jacket is reduced, atmospheric pressure holds the material closely to the skin at the arm, neck, and pelvis, effecting a satisfactory seal Special cuffs are provided to ensure a good seal at the arms, and an inflatable bag over the pubic region assists in obtaining a seal at the lower end of the jacket, especially if the patient has a scaphoid abdomen

To prevent moisture from condensing inside the jacket, as might happen if it were totally impervious, the cloth used permits some air to leak through it at each respiration We have also used an airtight plastic jacket and are informed that jackets impervious to various degrees are to be had

Pump

The makers supply a pump based on a Rootes-type air-pump The pump unit is small, 22×10½×21 in , so that it can readily be used for travelling Accessories are available so that it can be powered by batteries, and there is a hand-operated pump for emergencies which, when it is not in use, serves as a storage cabinet For ward use the pump is run from the electric mains and is housed in a silencing cabinet It then emits a high-pitched sound which is not loud but, where there is little background noise, irritates some people

Efficiency as a Breathing-machine

The Tunnicliffe breathing-jacket has been used on patients with poliomyelitis or myasthenia gravis, of ages from 6 to 54 years, as well as on healthy people Its efficiency was compared with that of a cuirass and that of I P P R

The patients already had a tracheotomy with a cuffed tracheotomy tube (Spalding and Smith 1956) The cuff was inflated during the tests, preventing leakage of air through nose and mouth The neck seal was adjusted to clear the tracheotomy, and this may slightly have affected the performance of the jacket A low-resistance valve-system was plugged into the tracheotomy tube and insured that the patient inspired from the atmosphere and expired through a gas-meter (Parkinson and Cowan 'Type C D')

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* Supplied by Electronic and X-ray Applications, Ltd , 13, Pennant Mews Kensington, London W 8

Fig 2 shows the results of such a test in a woman of 30 who had developed poliomyelitis six weeks previously Her diaphragm was active, but her intercostal muscles were very weak, and her vital capacity was only 480 c cm To assess how much each apparatus assisted the patient she was instructed to take five deep breaths in time with the machine, which was running at 16 respirations per minute, and these breaths were measured Fig 2 shows the assisted vital capacity achieved in this way with breathing-jacket, cuirass, and I P P R at various inspiratory pressures The cuirass added only a little to the vital capacity, the breathing-jacket was considerably more effective, and I P P R was the most effective

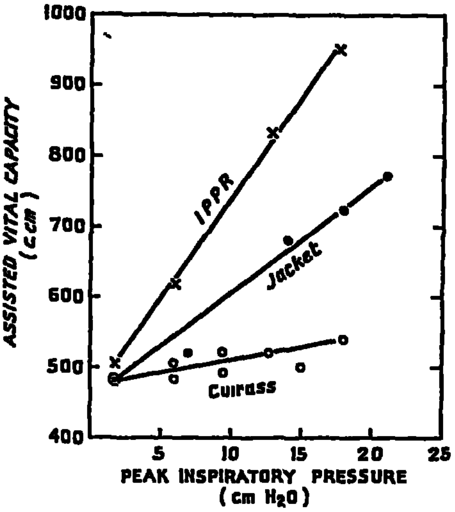

Fig 2—Assisted vital capacity of patient with poliomyelitis at various peak inspiratory pressures with I P P R, breathing-jacket, and cuirass

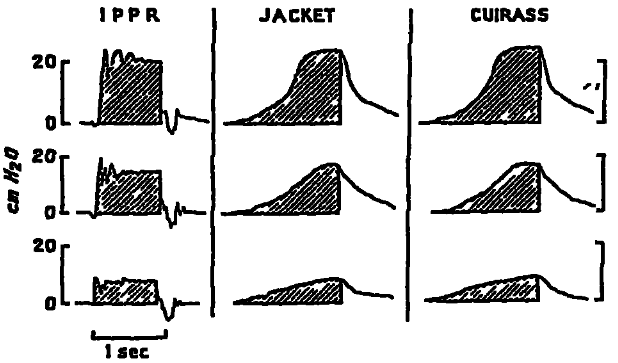

Fig 3—Records taken during examination shown in fig 2, showing rise of pressure in trachea relative to that applied to skin of chest and abdomen during inspiration by I P P R, with breathing-jacket, and with cuirass Inspiratory period is hatched

In all methods of artificial respiration considered here (and in the tank respirator) inspiration takes place because the pressure in the trachea is higher than the pressure on the surface of the trunk In I P P R this is achieved by raising the tracheal pressure above atmospheric pressure in the other methods it is achieved by reducing the pressure on the trunk below atmospheric pressure When the data shown in fig 2 were obtained, pressure tracings were recorded from within the jacket or cuirass or, during I P P R, from the trachea

Fig 3 is taken from the tracings and shows the inspiratory rise in the pressure in the trachea relative to that on the surface of the chest and abdomen for the three types of artificial respiration The pressure wave-form is different in the three machines With I P P R the wave-form is approximately square, which is a particularly efficient wave-form (Spalding and Young 1955), but the duration of inspiration is less than with the jacket and the cuirass

An alternative standard of comparison may be obtained by considering the mean pressure during inspiration (fig 4) rather than the peak pressure On this basis the performance of the breathing-jacket approximates more closely to that of I P P R, especially at low pressures, and the benefit of the jacket compared with that of a cuirass remains considerable

It is important, when the jacket is applied, that a large enough shell be used Fig 5 shows observations on a patient with myasthenia gravis causing respiratory weakness At first (curve A) a considerable increase in the pressure produced little change in the tidal air The breathing-jacket was, however, touching the anterior abdominal wall during inspiration, and, when the test was repeated after correction of this fault, the results shown in curve B were obtained

Discussion

I P P R, like respiration in a tank respirator, is mechanically a very efficient method of artificial respiration (Bourdillon et al 1950, Spalding 1955, Spencer 1957) and therefore a suitable standard of comparison The Tunnicliffe breathing-jacket lies intermediate in efficiency between I P P R and the cuirass, and the useful advantage it shows over the cuirass is attributable to the freedom it permits to the thoracic cage, so that not only is the rib-splinting effect of the cuirass eliminated but also subatmospheric pressure within the jacket can act on almost the whole mobile part of the chest and abdomen The difference between the breathing-jacket and I P P R is probably due to the slight contact of the jacket with the upper chest wall and lower abdomen

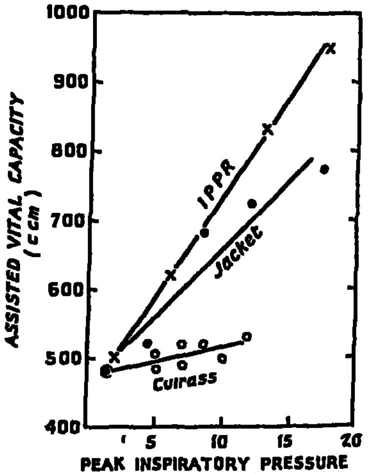

Fig 4—Assisted vital capacity at various mean inspiratory pressures with I P P R, breathing-jacket, and cuirass

The wave-form of the pressure tracings was similar whether the jacket or the cuirass was used, but with I P P R it was of the square-wave type It is difficult to be precise when comparing artificial respiration with different wave-forms The effect of the difference, however, can be minimised by considering the mean rather than the peak inspiratory pressure, and in this instance, when the mean pressure is considered, the jacket and cuirass, in which the inspiratory period is longer than with I P P R, are probably unduly favoured Nevertheless the overall comparison of jacket, I P P R, and cuirass is not seriously altered in whichever way the comparison is made

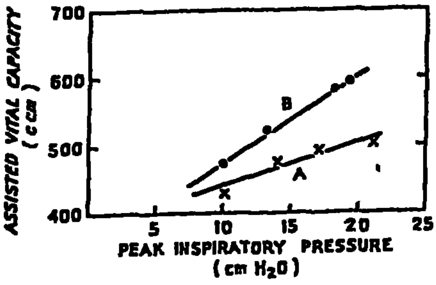

Fig 5—Tidal air of patient with myasthenia A with plastic shell too tight, B, with plastic shell correct

This investigation indicates that this breathing-jacket is efficient and is a valuable addition to the apparatus for artificial respiration In paralysing disease it is especially suitable for weaning patients with considerable respiratory weakness, especially of the intercostal muscles It should also be particularly well suited for transporting such patients long distances, by air or on the surface In another field its efficiency and reliability should render it useful for maintaining respiration during bronchoscopy with relaxants and permit the bronchoscopist to examine the bronchial tree without being interrupted by the need to inflate the patient at intervals

Summary

The Tunnicliffe breathing-jacket is described, and its efficiency as a breathing-machine is compared with that of intermittent positive-pressure respiration and that of the cuirass

The breathing-jacket can be substantially more effective than the cuirass, but less so than I P P R

The differences are attributed to the relative freedom from restriction to the chest and abdomen in the three methods

The breathing-jacket should prove useful in weaning paretic patients from tank respirators and I P P R, in transporting patients with a respiratory paralysis or paresis, and in maintaining respiration during bronchoscopy when a relaxant is used

We are grateful to Dr W Ritchie Russell for much helpful criticism and to Mr E J Tunnicliffe, of Electronic and X-ray Applications, Ltd, 13, Pennant Mews, Kensington, London, W 8, for the loan of breathing-jackets and pump

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AUTOGENOUS VACCINE IN PROPHYLAXIS OF THE COMMON COLD

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IN the early 1930s, shortly after the municipal laboratory in Birkenhead was opened, requests for vaccine treatment were made by clerks of the health department who had been chronic sufferers from the common cold These were refused, on the ground that, since colds were due to a virus, the treatment would necessarily be useless

One woman, however, who had had one continual " cold " for several winters, was very persistent in her appeals for a vaccine, though told repeatedly that no benefit could follow Ultimately a vaccine was made from her saliva, and she was plainly told that it was being given to her only to prove its uselessness She had weekly injections throughout the following winter, and had no cold Though told that that had been a pure coincidence, she presented herself, with several others, for a further vaccine at the end of the following summer Autogenous vaccines were not refused, but it was strongly explained to all that no possible effect could be expected All experienced a winter free from cold, though some had the prodromal stages

It was felt that this continued result was a strange coincidence but nothing more For some years a small but steady stream of clerks and police were treated, more or less unwillingly, by the laboratory Though no special investigations were possible, it gradually became apparent that, over a period of some twenty years, in which 60 or 70 people were vaccinated, almost the only failures were some cases of long standing, where it was practically certain that degenerative changes had taken place in the mucous membrane In a few cases the improvement might be explained on psychological grounds, but the series was becoming too long for this explanation to be sufficient

As a result of these and other findings, the opinion was formed that the common cold might be due to two factors —the virus, whose function is essentially depressive, and an invasion by the patient's own normal but heterogeneous secondary organisms, which are usually present in a state of equilibrium, overstepping the mark only as a result of the patient's depressed resistance caused by the virus If this explanation was correct, these volunteers, experiencing the prodromal stage for a day or two, still kept on taking their colds as far as the virus was concerned, but were immunised against the effects of their own organisms If patients could be protected against these, the virus could do its worst, causing only slight nasal inconvenience In support of this explanation was the fact that penicillin lozenges were by then known to clear up colds in certain persons only, being useless in others—depending presumably on the sensitivity of the patient's own flora Similar support was given by the unreliable results of stock vaccines which were possibly of value only where the stock strains were the same as the patient's own

Investigation

In the spring of 1955 permission was obtained to carry out a preliminary investigation in a series of volunteers Dr J N MacDonald, the principal medical officer of Lever Brothers, Port Sunlight, was approached with a view to getting volunteers among the staff there From the very beginning the utmost cooperation was shown by him and his staff, and it was decided to carry out an investigation It was agreed that 200 volunteers should be asked for, of whom 80 would be controls This entailed giving a series of injections to the whole 200, of whom 120 received an autogenous vaccine and 80 carbol saline only 109 of the vaccinated and 75 controls completed the investigation

Selection of Controls

A series of 80 numbers was selected by a method which gave an apparently completely haphazard spread It was agreed that these figures should be kept confidential by the laboratory Volunteers were to be numbered in strict rotation, and samples taken from all If, however, a volunteer's number happened to coincide with one of the 80 numbers previously selected, no vaccine was to be made, instead a bottle was prepared with carbol saline only

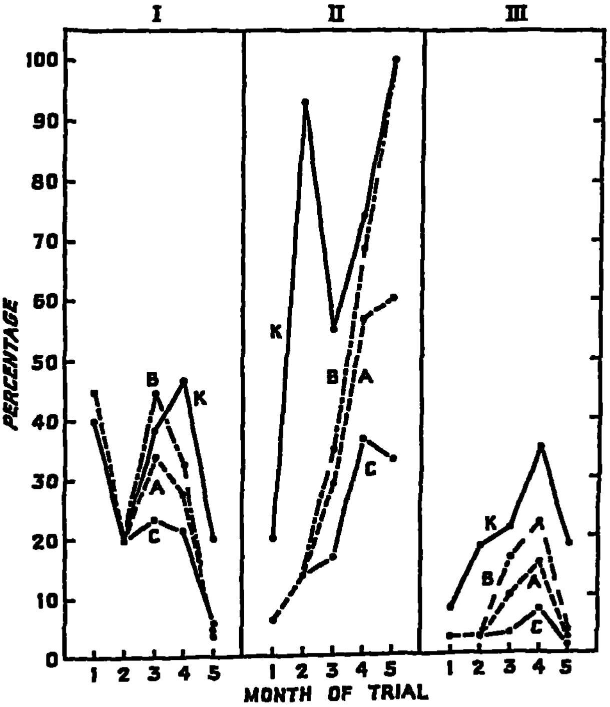
To exclude the possibility of bias, information was sought about age, sex, years of service at the works, association with children, and smoking The only one of these which gave an appreciable difference in distribution between the vaccinated and control groups was the proportion of smokers In the vaccinated the numbers of smokers and non-smokers were about equal, while in the controls non-smokers outnumbered smokers by almost two to one If anything this should predispose the vaccinated group towards a higher incidence of colds

Technique of Preparation of Vaccine

During the period May–July, 1955, swabs were taken from throat and nose, and volunteers were asked to clear the throat and spit into a 1 oz universal container When a volunteer was to be a control, swabs and saliva were discarded on arrival at the laboratory Specimens were plated on blood-agar, one plate being used for saliva and the two halves of another plate for throat and nose swabs Much the best growths were obtained from the saliva After incubation overnight at 37°C, cultures were rubbed off into carbol saline in 1 oz screw-capped containers, no attempt at selection being normally made Hæmolytic streptococci were found on the plates in a few cases only, and in these cases fresh samples were obtained, as this organism can hardly be classed with the normal nasopharyngeal inhabitants In each case repeat culture showed that the hæmolytic streptococci had disappeared, and the later cultures were used to make the vaccine A similar step was taken where a mould interfered with emulsification These were the only routine attempts at selection and were merely precautionary A loopful of emulsion was stained by Gram's method The container was immersed totally in a water-bath at 60°C for an hour to kill the organisms, and the sample was further emulsified as far as possible by fifteen minutes in the Kahn shaker The final suspension was made directly into a numbered vaccine bottle to a strength of about 500 million per ml After a sterility test, vaccines were stored in the refrigerator until September, in numerical order with the control solutions in exactly similar vaccine bottles It had been intended to begin the trial earlier, but, because of the prolonged good weather in 1955, a start was delayed by about a month

Cultural Findings

No attempt was made to identify individual organisms This had been tried years before, with very diverse results In the present work *Streptococcus viridans* appeared to predominate in about four-fifths of the volunteers Even these, however, were heterogeneous A few staphylococci were also found Only one strain of *Staphylococcus aureus* was seen, this came from a patient who had recently had a suppurative lesion of the nose This strain was discarded, and not used for the vaccine Diphtheroids were less common than had been expected, and were plentiful in only 6 cases *Neisseria catarrhalis* were numerous in about half the cases



I—No of total incidents (*a*+*b*+*c*) per 100 volunteers in each month of trial in each group

II—Percentage of total incidents (*a*+*b*+*c*) going on to full colds (*a*)

III—No of full colds (*c*) per 100 volunteers
A=all vaccinated B=vaccinated only for first eight weeks
C=vaccinated throughout five months K=controls

TABLE I—FIRST (TO MID-NOVEMBER) AND SECOND (TO MID DECEMBER) MONTHS OF TRIAL

—	First month		Second month	
	A	K	A	K
No of volunteers	109	75	109	75
Colds				
'Full' (*a*)	3 (*3%*)	6 (*8%*)	3 (*3%*)	14 (*18%*)
"N S T" (*b*)	1 (*1%*)	1 (*1%*)	5 (*5%*)	0 (*0%*)
Prodromal (*c*)	45 *41%*)	23 (*31%*)	14 (*13%*)	1 (*1%*)
No of incidents (*a*+*b*+*c*)	49 (*45%*)	30 (*40%*)	22 (*20%*)	15 (*20%*)
(*a*)/(*a*+*b*+*c*)	3/49=6%	6/30=20%	3/22=14%	14/15=93%

A=vaccinated K=controls

Administration of Vaccine

The first dose was invariably 0 1 ml Controls were dealt with in exactly the same way as those receiving the vaccine itself A sheet of instructions was given to each volunteer, asking him or her to report to the health centre in the firm's premises if any reaction, however trivial, was experienced Doses were repeated at intervals of a week The second dose was 0 3 ml, and the third and subsequent doses 0 5 ml, but when there was a reaction to the initial dose, the next was reduced to 0 2 or 0 1 ml

Reactions

These were of three types

1 There was local redness at the site of inoculation in 71 of the vaccinated volunteers (65%) and in 9 (12%) of the controls This difference between vaccinated and controls was kept confidential and in fact denied when any hints or surmises were made The area of redness was usually $^1/_2$–1 in in diameter, mildly tender for a day or two, and then subsiding In a few of the vaccinated an area of redness developed several inches across The larger reactions were usually in volunteers who were definitely subject to colds These local reactions were commoner in this series than they had been in previous volunteers, and more marked in females than in males

2 About a dozen volunteers reported that after the inoculation they had experienced a feeling of dryness in the throat with some headache, as if they were beginning to take a cold This lasted for a day or so and then passed off This reaction was confined to those who were given the vaccine

3 A few patients reported at the second inoculation that they had been beginning a cold at the time of their first Some said that the inoculation had aggravated the condition, and one or two promptly retired from the investigation Others thought that the inoculation had helped to clear it up Each of these categories included both vaccinated and control volunteers Wishful and muddled thinking is difficult to eliminate *It was felt that these early reactions were essentially unreliable, and that the effect of the vaccine would have to be judged by the incidence of colds during the winter*

Course of the Investigation

In view of the difficulty of estimating what different people mean by the severity of a cold, no effort was made to classify "incidents" beyond three main groups *All clinical assessment was carried out by the staff of Port Sunlight, entirely independently of the laboratory, they did not know until the investigation was over which volunteers had had vaccine* Incidents were classified *after a combination of patients' statements and the findings of the health staff* It is considered that with their knowledge of the patients a reasonable degree of accuracy was attained

Incidents were classified thus

(*a*) Colds, unmodified (–"*Colds, full*")

(*b*) Colds, "not so toxic" (-"Colds, N S T") This is where further symptoms (e g, mucopurulent discharge) developed for a day or two only, and the patient *volunteered* the statement that the cold was milder and or shorter than was

TABLE II—THIRD (TO MID-JANUARY), FOURTH (TO END OF FEBRUARY) AND FIFTH (TO END OF MARCH) MONTHS OF TRIAL.

—	Third month				Fourth month				Fifth month			
	Vaccinated			Controls	Vaccinated			Controls	Vaccinated			Controls
	A	B	C	K	A	B	C	K	A	B	C	K
No of Volunteers	109	58	51	75	109	58	51	75	109	58	51	75
Colds												
Full (*a*)	11 (*10%*)	9 (*16%*)	2 (*4%*)	16 (*21%*)	17 (*16%*)	13 (*22%*)	4 (*8%*)	26 (*35%*)	3 (*3%*)	2 (*3%*)	1 (*2%*)	15 (*20%*)
“ N S T ” (*b*)	8 (*7%*)	6 (*10%*)	2 (*4%*)	4 (*5%*)	4 (*4%*)	1 (*2%*)	3 (*6%*)	5 (*7%*)	1 (*1%*)		1 (*2%*)	
Prodromal (*c*)	19 (*17%*)	11 (*19%*)	8 (*16%*)	9 (*12%*)	9 (*8%*)	5 (*9%*)	4 (*8%*)	4 (*5%*)	1 (*1%*)		1 (*2%*)	
$a+b+c$	38 (*35%*)	26 (*45%*)	12 (*24%*)	29 (*39%*)	30 (*28%*)	19 (*33%*)	11 (*22%*)	35 (*47%*)	5 (*5%*)	2 (*3%*)	3 (*6%*)	15 (*20%*)
$a/(a+b+c)$	11/38 = 29%	9/26 = 35%	2/12 = 17%	16/29 = 55%	17/30 = [illegible]	13/19 = 68%	4/11 = 36%	26/35 = 74%	3/5 = 60%	2/2 = 100%	1/3 = 33%	15/15 = 100%

expected, perhaps suddenly clearing up. When this stage developed in the vaccinated, there was usually a history of frequent colds in the past, and this reduced toxicity was generally confirmed by the health records available. On the other hand, this category was not entirely absent from the controls.

(*c*) Prodromal stages only (=“ Prodromal ”). This is strictly confined to the initial stages—i.e., up to a non-purulent running nose for two days (rarely three) with no further symptoms whatever, and no apparent toxicity. This stage corresponds to what, it is suggested, may be due to the virus infection itself.

The clinical course was divided into sections of about a month each. It was assumed that, with this interval, each incident could be regarded as a separate infection, and therefore was entered in each period as it happened irrespective of a volunteer's history in any previous month.

First month of trial.—The first month is included (table I), though not much can be deduced from the figures, as the investigation was only settling down and emotional elements could not be entirely eliminated. The higher percentage of prodromal stages in the vaccinated than in the controls may be due to the inclusion of a number of early reactions. Some of the records in both prodromal groups may be of emotional origin.

Second month of trial.—This period (table I) shows a very close relationship between the vaccinated and the controls in the percentage showing incidents. This again is consistent with the explanation that the prodromal stages are due to the virus and unaffected by vaccination. The cold-rate among the workers outside the trial was also high, estimated by the health-centre staff at about one in five. The ratio $a/(a+b+c)$, however, shows a striking difference between the vaccinated and the controls.

At this stage it became plain that, while the utmost cooperation was being shown by the staff at Port Sunlight, considerable inconvenience was being caused to certain departments. It was therefore decided that, unless a volunteer definitely desired to carry on, inoculations might cease after eight weeks. Vaccinated and controls ceased injections in approximately equal proportions throughout the departments, and it is felt that if an element of selection had occurred those electing to continue would be those most prone to develop colds. They should therefore show a higher percentage of “ full colds ”, whereas they showed markedly less. About half of the volunteers carried on, and they received weekly injections until their vaccine (or control) bottle was empty. This period varied considerably, as it depended on the volume of the suspension, which in turn depended on the opacity of the original emulsion. In a few cases, a fresh vaccine was made.

For the further periods, therefore, separate figures have been prepared for those who for one reason or another received eight or fewer injections (group B) and for those receiving the full course (group C). (A similar proportion of controls stopped injections, but they are not distinguished in the tables.)

TABLE III—COLD-RATE (FULL COLDS ONLY) PER MONTH PER VOLUNTEER (UPPER PART), COLD-RATE IN LAST 3 MONTHS AMONG CERTAIN VOLUNTEERS PREVIOUSLY SUBJECT TO FREQUENT OR HEAVY COLDS (LOWER PART)

Group	Month	Vaccinated						Control	
		A		B		C		K	
		Vols	Colds	Vols	Colds	Vols	Colds	Vols	Colds
All vols	1	109	3 (*3%*)			109	3 (*3%*)	75	6 (*8%*)
	2	109	3 (*3%*)			109	3 (*3%*)	75	14 (*19%*)
	3	109	11 (*10%*)	58	9 (*16%*)	51	2 (*4%*)	75	16 (*21%*)
	4	109	17 (*16%*)	58	13 (*22%*)	51	4 (*8%*)	75	26 (*35%*)
	5	109	3 (*3%*)	58	2 (*4%*)	51	1 (*2%*)	75	15 (*20%*)
	Total	545	37 (*7%*)	174	24 (*14%*)	371	13 (*4%*)	375	77 (*21%*)
Cold-prone vols	3	25	1	9	1	16	0	12	5
	4	25	2	9	1	16	1	12	3
	5	25	0	9	0	16	0	12	1
	Total	75	3 (*4%*)	27	2 (*7%*)	48	1 (*2%*)	36	9 (*25%*)

Vols = volunteers

Third month of trial (table II).—While the percentage of total incidents remained very similar in the vaccinated (35) and controls (39), the figures in column C are very different from those in column K. Column A in table I is of course comparable now to column C.

Group B had a relatively higher incidence-rate, but the ratio $a/(a+b+c)$ was still well below that shown in group K. It

TABLE IV—ABSENCE FROM WORK ATTRIBUTED TO “ COLDS ” AND “ UPPER RESPIRATORY INFECTIONS ”

—	1954–55					1955–56				
	Vaccinated			Controls	Total	Vaccinated			Controls	Total
	A	B	C	K	A+K	A	B	C	K	A+K
Colds										
No of days off	45	26	19	35	80	55	40	15	110½	165½
„ „ persons	109	58	51	75	184	109	58	51	75	184
Days off per person	0·41	0·45	0·37	0·47	0·43	0·50	0·69	0·29	1·47	0·90
Increase or decrease						+22%	+53%	−21%	−213%	−110%
Upper respiratory infections										
No of days off	229	117	112	105	334	298	219	69	266	564
„ persons	109	58	51	75	184	109	58	51	75	184
Days off per person	2·1	2·0	2·2	1·4	1·8	2·7	3·8	1·4	3·5	3·1
Increase or decrease						+29%	−90%	−36·4%	−150%	+72%

seems, however, that group B stopped too soon and received only temporary protection

Fourth and fifth months of trial (table II)—The findings resemble those of the third month It appears that protection was incomplete when injections ceased at the eighth week, but good in those who continued This is compatible with the opinion on which the investigation is based

Discussion

The results indicate that the vaccination protected a full-cold volunteer in whom prodromal symptoms appeared

Moreover, table III shows that there was a difference in the cold-rate between groups C and K The figures suggest that some form of protection was conferred by the vaccines, which was lost if treatment stopped too soon The results in group B suggest that protection disappears some time after the injections are stopped, if true, this is strong evidence that such protection exists

Absence-rates—Table IV shows the number of days lost by volunteers during October–March, 1955–56, compared with the rates in the same period in 1954–55 The increase in absence-rate of 1955–56 over 1954–55 was general throughout the staff at Port Sunlight and is not confined to the volunteers of this investigation

The difficulty of knowing what to include as a " cold " has been met by distinguishing cases where absence was attributed to a " cold " by the practitioner or health records from those where it was attributed to " upper respiratory infections " (i e , including tonsillitis, influenza, bronchitis, as well as colds) The trend in both is similar

Summary

Clinical observations suggest that the common cold is due to two factors

1 The virus, which acts by depressing resistance, so upsetting the normal balance, and leading to

2 Attack by the nasopharyngeal flora, heterogeneous but fairly constant in an individual patient This second stage is responsible for most of the distressing symptoms

184 volunteers were observed in the winter of 1955–56, 109 were given weekly injections of autogenous vaccines from their own nasopharyngeal flora and 75 were given carbol saline only

The cold-rate per month for the controls was five times that of those who were vaccinated throughout the course The rate of absence from work through " colds " and " upper respiratory infections " was also greater in the controls

During the investigation the percentage of colds passing from the prodromal to the fully developed stage was 13 in volunteers continuing vaccine and 62 in the controls

The number of volunteers continuing injections was 109 for each of the first two months, and 51 for each of the next three—i e , a total of 371 volunteer/months for the whole period The corresponding figure for the controls was a constant 75 for each month—i e , a total of 375 volunteer/months In the vaccinated there were 13 full colds in the 371 volunteer/months as against 77 in 375 volunteer/months in the controls

I am grateful to Dr J N MacDonald of Lever Brothers, Port Sunlight, and his staff for their very valuable cooperation in assessing the results Particular thanks are due to Sister P Gates of the staff there for her encouragement and ready help in ascertaining quantities of data of various kinds

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ANTIBIOTICS IN SMALL DOSES FOR THE COMMON COLD

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I BELIEVE that most symptoms of the common cold are caused by relatively enhanced virulence of the patients' normal nasal and pharyngeal flora following depression of his resistance by the virus To test this hypothesis, I carried out an investigation during the winter of 1955–56 volunteers receiving weekly injections of autogenous vaccine were compared with controls who received carbol saline only The results were encouraging in that the cold-rate in those vaccinated throughout the course was only a fifth of that in the controls, and the rate of absence from work through " colds " or " upper respiratory infections " was also lower

Mass vaccine treatment is impracticable, and I decided to try the effect of short-term controlled antibiotic therapy, after ascertaining the sensitivity of the patient's pharyngeal flora before the winter began If vaccines had given a degree of active immunity, then suitable antibiotic tablets, given to suck at the beginning of the prodromal stage, might well give sufficient passive protection by depressing the pharyngeal flora temporarily to correspond to the depression of the patient's resistance To avoid risk of producing insensitive strains of bacteria or of disturbing permanently the balance normally maintained between patient and pharyngeal flora, I decided to try the effect of brief local application only

Details of Investigation

After preliminary trials had shown that the sucking of lozenges did in fact reduce the numbers of pharyngeal flora, and that this effect was temporary, invitations to cooperate were sent out through the medical officers concerned to some of the larger works in the neighbourhood Several indicated willingness, as did a boarding-school and the Chief Constable of Birkenhead Altogether 1043 volunteers took part, 919 completed the investigation itself

Cultural Tests

The same general routine was adopted with all, on similar lines to that previously followed with the autogenous vaccines

In the latter part of 1956 samples of saliva were collected in screw-capped containers, and a sensitivity test on blood-agar was carried out on each, overnight at 37°C, using Evans ' Sentests', against penicillin, streptomycin, chloramphenicol, aureomycin, oxytetracycline, erythromycin, and tetracycline A loopful of culture was stained by Gram's method, and the diameter of the zones of inhibition was noted As in the previous investigation, a high percentage of *Streptococcus viridans* was observed Very few hæmolytic streptococci were seen, and where this organism was found records were not made until on repeat culture it had disappeared Non-hæmolytic streptococci were common *Staphylococcus aureus* was practically absent, and diphtheroids were not numerous Moulds and yeasts were few, where they did not interfere with the sensitivity tests they were ignored A curious feature was that different areas produced, each for itself, a more or less similar distribution of organisms

As selection of bacteria is impossible in the use of antibiotics in the field, it followed that this could not be attempted in the investigation Therefore, the antibiotic findings were recorded merely by the diameter of complete apparent (visual) inhibition of bacterial growth

Controls

In the first place, although sensitivity tests were done on all, every 4th volunteer was designated a control Next, some volunteers, on whose cultures sensitivity-test results could not be recorded, were relegated to the controls, as this was administratively easier than to have some odd repeat specimens from the outside works These were 31 in all and were divided thus

No saliva in container	8
No growth on plates	7
Unreadably poor growth	4
Culture overgrown by yeasts	7
" " " coliforms	5

In none of these could sensitivity be assessed, but as sensitivities were readily estimated in all others (over 1000) it seemed reasonable to assume that these 31 would follow the average pattern, though hidden by circumstances In no case was a culture put in this category because it gave poor sensitivity rings

The age and sex distribution and smoking habits of the controls were similar to those of the other volunteers

The Tablets

In so few cases did penicillin and erythromycin give the best inhibition rings that it was not worth while considering them for the test itself Streptomycin was little better Chloramphenicol gave the best ring in many cases, but its bitterness ruled it out entirely Those left were aureomycin, oxytetracycline, and tetracycline The sensitivity rings tended to differ, and it was deemed advisable to treat each as a separate entity

Four types of lozenge were obtained from the manufacturers containing severally tetracycline 15 mg , oxytetracycline 15 mg , aureomycin 15 mg , and an inert substance (glucose) Each type was given a number, and a card bearing a number was prepared for each volunteer—that of the inert lozenge for the controls and that of the appropriate antibiotic (according to the sensitivity tests) for the others The significance of each number was not known outside the laboratory

Recording of Results

Health-centre personnel were taken as they were and the set-up varied slightly from works to works Where there was a full-time doctor or trained nurse in charge, it was felt that results could be entirely relied upon At the boarding-school the matron functioned as health centre, with a visiting doctor In the case of the police the laboratory had to act as medical centre, since assessment would necessarily be done in consultation with someone who knew which would be controls, the police results were kept in a separate category and used as a day-to-day assessment of how the investigation was proceeding

Dosage

This was purely empirical To avoid the chance of ill effects, the very small dosage of two tablets a day for two days was tried It became plain from the police reactions that the original cautious dosage was in some cases too small Several policemen, after having two tablets a day for two days, reported that, while they thought the tablets were working, they still felt that a cold might develop, and a few were given another couple of tablets with good results In the later stages of the trial a dosage of two a day for not more than three days was allowed when required No policeman reported any untoward results of the increased dosage Another point which emerged was that, to have maximal effect, treatment should be begun on the day that the earliest symptoms were noticed

If the prodromal stages began, for example, on a Friday or a Saturday, treatment begun on the Monday might give little or no result, though if treatment began early enough good results were obtained This finding is reasonable, as the trial of short-term antibiotics here was to forestall the attack of the pharyngeal flora, and in these late cases that attack had already developed

The Trial Itself

The tablets were issued to the works health centres, where volunteers were given them when they reported prodromal symptoms To keep the test as free from prejudice as possible, there was no communication whatever between the laboratory and the medical centres, from the time the investigation started in the autumn until it was finishing about Easter, except for the supply of further tablets, and a single authorisation from the laboratory to proceed beyond the original maximum of four tablets The assessments were collected by the

NUMBER OF VOLUNTEERS AND INCIDENTS IN EACH GROUP

—	Police		Metal Works (1)			Oil Derivatives			Metal Works (2)		Carbon Works			Flour mill †			Large office			Boys boarding school		All except police		
	A	B	A	B	K	A	B	K	B	K	A	B	K	A	B	K	A	B	K	B	K	A	B	K
No of Volunteers (*V*)	27	26	124	123	61	125	113	75	• 122	71	77	73	54	68	67	40	38	35	15	‡ 48	22	432	581	338
Colds (*a*)	3	1	9	5	20	21	5	21	0	14	4	2	11	5	2	3	4	0	4	8	14	43	22	87
N S T (*b*)	2	1	5	3	2	11	4	7	2	3	2	1	1	2	0	0	0	0	0	10	10	20	20	23
Prodromal (*c*)	6	6	45	45	5	48	48	17	68	16	11	11	6	29	29	12	18	18	5	26	11	151	245	72
Incidents ($a+b+c$)	11	8	59	53	27	80	57	45	70	33	17	14	18	36	31	15	22	18	9	44	35	214	287	182
$\frac{a}{a+b+c}$	$\frac{3}{11}$	$\frac{1}{8}$	$\frac{9}{59}$	$\frac{5}{53}$	$\frac{20}{27}$	$\frac{21}{80}$	$\frac{5}{57}$	$\frac{21}{45}$	0	$\frac{14}{33}$	$\frac{4}{17}$	$\frac{2}{14}$	$\frac{11}{18}$	$\frac{5}{36}$	$\frac{2}{31}$	$\frac{3}{15}$	$\frac{4}{22}$	0	$\frac{4}{9}$	$\frac{8}{44}$	$\frac{14}{35}$	$\frac{43}{214}$	$\frac{22}{287}$	$\frac{87}{182}$
%	27	13	15	9	74	26	9	47	0	42	24	14	61	14	6	20	18	0	44	18	40	20	8	48
$\frac{c}{a+b+c}$	$\frac{6}{11}$	$\frac{6}{8}$	$\frac{45}{59}$	$\frac{45}{53}$	$\frac{5}{27}$	$\frac{48}{80}$	$\frac{48}{57}$	$\frac{17}{45}$	$\frac{68}{70}$	$\frac{16}{33}$	$\frac{11}{17}$	$\frac{11}{14}$	$\frac{6}{18}$	$\frac{29}{36}$	$\frac{29}{31}$	$\frac{12}{15}$	$\frac{18}{22}$	$\frac{18}{18}$	$\frac{5}{9}$	$\frac{26}{44}$	$\frac{11}{35}$	$\frac{151}{214}$	$\frac{245}{287}$	$\frac{72}{182}$
%	55	75	76	85	19	60	84	38	97	49	65	79	33	81	94	80	82	100	56	59	31	71	85	40
$\frac{a+b+c}{V}$	$\frac{11}{27}$	$\frac{8}{26}$	$\frac{59}{124}$	$\frac{53}{123}$	$\frac{27}{61}$	$\frac{80}{125}$	$\frac{57}{113}$	$\frac{45}{75}$	$\frac{70}{122}$	$\frac{33}{71}$	$\frac{17}{77}$	$\frac{14}{73}$	$\frac{18}{54}$	$\frac{36}{68}$	$\frac{31}{67}$	$\frac{15}{40}$	$\frac{22}{38}$	$\frac{18}{35}$	$\frac{9}{15}$	$\frac{44}{48}$	$\frac{35}{22}$	$\frac{214}{432}$	$\frac{287}{581}$	$\frac{182}{338}$
%	41	31	48	43	44	64	50	60	57	47	22	19	33	53	46	38	58	51	60	92	159	50	49	54
$\frac{a}{V}$	$\frac{3}{27}$	$\frac{1}{26}$	$\frac{9}{124}$	$\frac{5}{123}$	$\frac{20}{61}$	$\frac{21}{125}$	$\frac{5}{113}$	$\frac{21}{75}$	0	$\frac{14}{71}$	$\frac{4}{77}$	$\frac{2}{73}$	$\frac{11}{54}$	$\frac{5}{68}$	$\frac{2}{67}$	$\frac{3}{40}$	$\frac{4}{38}$	0	$\frac{4}{15}$	$\frac{8}{48}$	$\frac{14}{22}$	$\frac{43}{432}$	$\frac{22}{581}$	$\frac{87}{338}$
%	11	4	7	4	33	17	4	28	0	20	5	3	20	7	3	8	11	0	27	17	64	10	4	26

A no of volunteers reporting incidents B, no reporting incidents, excluding those known to have reported late and developed a full cold.
K no of controls
• At this works latecomers were rigidly excluded. † This works closed down before the cold season had properly begun
‡ It was hard to assess the time of the start of the symptoms in these boys

laboratory when the investigation was over, they were made by

Metal works (1) Oil derivatives	Full time doctor and qualified nurses
Metal works (2) Carbon works	Part-time doctor and full time nurses
Flour mill	Part time doctor and deputy manager
Large office Boys boarding-school	Part-time doctor and full time matron

Unfortunately, no way of avoiding false alarms could be thought out, and it was realised that these were inevitable in the assessment of results little reliance has been placed on the total number of " incidents " by itself On the other hand, if my hypothesis is correct, it must follow that where there is a sufficiently high natural immunity against attack by secondary organisms there should be occasions when a cold is naturally cut short at the end of the prodromal stage It is, of course, a clinical fact that many " colds " do not develop, and therefore these prodromal stages cannot be ignored

When a statement was *volunteered* that though a cold was not entirely avoided it was much shorter or less troublesome than usual, it has been felt reasonable to include these as partially successful results which might have proved entirely so had dosage not been so carefully cut down These appear in the table as " N S T "—i e, not so toxic On the whole they were not numerous

Results

The proportion of the volunteers with prodromal symptoms who went on to a full cold was consistently much lower in the treated than in the control groups (see table)

Each report from a volunteer of the prodromal stage of a cold was recorded as an " incident " As there was no means of checking which of these were true colds, all were included in the belief that the drug and control groups would be evenly affected A volunteer was regarded as reporting a separate incident if the interval since the preceding one was about a month

As far as possible, note was kept of where a volunteer was late in reporting an incident, except in the control series This lateness had a definite effect on the results Records were kept of the number of " volunteers " (i e, the total number in each group), " Colds " (i e, incidents which developed into full colds), " N S T " (i e, the not-so-toxic colds), and " Prodromal " (i e, cases where the symptoms were cut short after a couple of days, with no mucopurulent stage following)

Discussion

There was a strong similarity in the findings of all the units of the investigation (see table), though there was no communication among them and the staffing arrangements varied considerably

The results in the office workers differed little from the factory results, though their conditions of work were entirely clerical

The nil returns in metal works (2), where latecomers seem to have been more rigidly excluded than elsewhere, are particularly encouraging However, there was also a nil return in column B for the office workers

The boarding-school with its totally different age-group and conditions, gave a different series of percentage ratios, but on broadly similar lines to the rest of the investigation The drop in the cold volunteer ratio (*a*/*V*) of four to one between the control and treated groups is for young boys highly encouraging, even though it was considerably below the average of the investigation, which showed a drop of six and a half to one Among the treated adult volunteers (excluding all latecomers), 14 colds developed in 533 volunteers (2 6 per 100), compared with 73 colds in 316 volunteers in the controls (23 1 per 100)—a ratio of one to nine

A difficulty experienced was that with some volunteers the antibiotics gave rise to unpleasant secondary effects Idiosyncracy appears to be a factor, as these untoward findings were by no means universal

It was, for example, not unusual to find that, while the cold cleared up readily in a couple of days, a period of astringent irritation, sometimes referred to as a sore throat or flayed tongue, might persist for a considerable time, somewhat on the lines of " penicillin tongue " This had been foreseen, but in order not to introduce any more factors into the investigation than could be helped, vitamins were not included Since this condition could be definitely unpleasant it seems that something on these lines is essential, and the matter is now being investigated The boarding-school, where vitamins are scientifically adjusted, had no trouble of this kind

Finally, to ascertain whether in fact the sensitivities of the mouth flora had remained stationary, repeat sensitivity-tests were done on 141 sputa after the investigation was completed On the whole, the later picture (May) was broadly similar to that in the same individuals in the autumn, and no trend was apparent in treated volunteers different from any in the controls, on the whole a change greater than 3 mm in diameter of the circle of inhibition was exceptional Again, changes were by no means always in the direction of reduced sensitivity

Conclusions

The results of this investigation seem to support the explanation that a patient's own pharyngeal flora bear a much larger share in the later disabling symptoms of the common cold than has hitherto been supposed The effect of autogenous vaccines in reducing the incidence of full colds in the vaccinated to a sixth of that found in controls has been duplicated by this series, using short-term controlled therapy by the appropriate antibiotic, wherein the incidence has been reduced nearly to a seventh of that in a series of controls, or, taking into consideration adults only, to a ninth It may well turn out that where a firm maintains a well-run medical centre which will cooperate with a laboratory, the disabling stages of the common cold may be as readily preventible as some of the other infectious diseases which are no longer a problem to the community

Summary

Investigations have been made on the supposition that the symptoms in the later stages of the common cold are due, not to the virus, but to the patient's own pharyngeal bacteria, which become relatively more virulent as a result of the depression of resistance by the virus infection

A series of tests was carried out on the effect of short-term controlled treatment with an antibiotic whose suitability for the patient had been previously ascertained by sensitivity tests

From October, 1956, until April, 1957, 919 volunteers were divided into two groups Of these, 581 received short-term antibiotic treatment when they felt a cold beginning, and 338 received an inert tablet In the treated

group, the number of prodromal stages reported was 287 (49%), of which 22 (7%) went on to full colds In the control group, the prodromal stages numbered 182 (54%), of which 87 (48%) went on to full colds—i e, 4 colds per 100 volunteers in the treated and 26 per 100 in the control group The figures for adults were 2 6 per 100 and 23 1 per 100 respectively

The small dosage of antibiotics used had no permanent effect on the sensitivity of the pharyngeal bacteria, nor on the proportions of the various species Some volunteers had irritation of the throat and tongue

It is suggested that, after sensitivity tests have been done, controlled short-term antibiotic therapy can without risk drastically cut down the effects of the common cold This method can easily be applied in industry by any well-staffed medical centre, cooperating with a laboratory

Thanks are due to Messrs Lederle and Messrs Pfizer for the supply of lozenges, to the medical officers of Williams and Willian Chester, Associated Ethyl Company Limited, Metal Containe Cabot Carbon, and Frost's Flour Mills (all in Ellesmere Por Messrs Littlewoods in Birkenhead, and Kingsmead School, Meo for their cooperation in the investigation, and to the Chief Constab of Birkenhead for permission to include members of his staff in the series

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PULMONARY MONILIASIS TREATED WITH NYSTATIN AEROSOL

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NOT uncommonly, fungi multiply rapidly during antibiotic therapy, more often in the intestinal than in the respiratory tract In the case reported here pulmonary moniliasis complicated a fulminating influenzal pneumonia and responded rapidly to inhalations containing nystatin

Case-report

A girl, aged 9 years, was admitted to the infectious diseases unit of St Ann's Hospital in the early hours of *Nov 18, 1957*, with a history of having started a "cold" forty hours previously When first examined by her own doctor seven hours before admission she had fever, a dry cough, and pain in the chest, but no other abnormal signs or symptoms Her general condition at that time was very good, but when she was seen again six-hours later she was found to be shocked, delirious, and grossly dyspnœic, and was immediately brought to hospital with a diagnosis of influenzal pneumonia By this time there were early signs of consolidation in her left lung She was put in an oxygen tent and given intramuscular penicillin and streptomycin together with sulphadiazine by mouth

When first seen by us fifty hours from the onset of her illness, she was unconscious, with facial twitchings, and extremely toxic, with respirations 76 per min, temperature 105°F, and pulse-rate 180 There were signs of pneumonia in both lungs, the left being worse than the right A white-cell count showed 3500 cells per c mm (polymorphs 2%, lymphocytes 96%) There was thought to be no doubt that this was a primary viral influenzal pneumonia of fulminating character, and the chances of recovery appeared remote Treatment with intravenous hydrocortisone 12 5 mg an hour was started, and the sulphadiazine was withheld.

Nov 19—Next day she was conscious and at times cooperative, and prednisone 5 mg six-hourly was substituted for the intravenous hydrocortisone Her general condition otherwise remained the same, with respirations 70 a minute No sputum could be obtained A white-cell count now showed 12,000 cells per c mm (96% polymorphs)

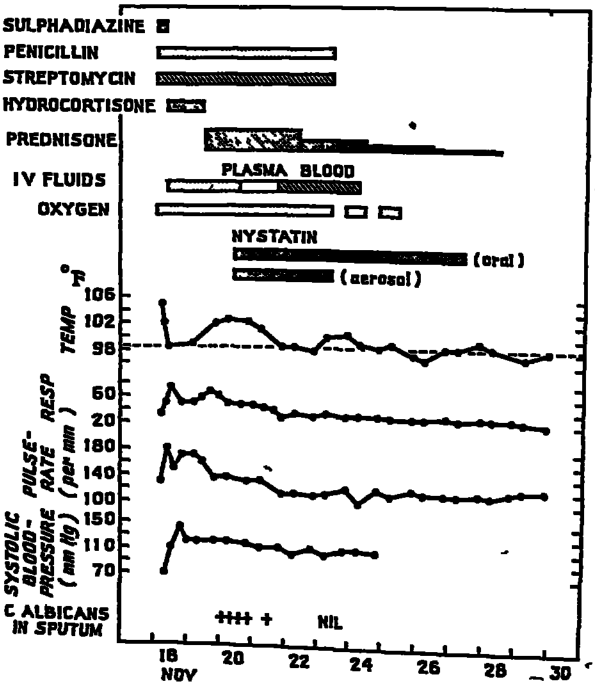
Nov 20—There was no change in the general condition, but the cough became productive for the first time, and large quantities of sticky blood-streaked mucogelatinous material were removed manually from the pharynx A direct film showed this to consist of epithelial cells and *Candida albicans* with no pus cells, and culture produced a heavy growth of *C albicans* This fungus was also recovered in profusion from the tongue, throat, fæces, and a perianal skin lesion which later developed, but blood-cultures were repeatedly sterile

Treatment with nystatin was started as soon as *C albicans* was seen on the sputum films 500,000 units was given six-hourly by mouth for eight days and 500,000 units four-hourly by nebuliser into the oxygen tent for four days The solution was made by mixing 500,000 units of 'Mycostatin' (Squibb) with 15 ml of distilled water to a fine suspension and atomising this at a flow of 6 litres a minute, which exhausted the solution in about an hour

Nov 21—Improvement began with lessening of the dyspnœa (respiration-rate 40–50 a minute) and the ability to take a little more by mouth

Nov 22—Extensive spontaneous emphysema appeared on the neck and the supraclavicular and left infraclavicular areas

Nov 23—The emphysema had spread over the whole chest, and a positive Hamman's sign confirmed the presence of mediastinal emphysema in addition (No distress was caused by this complication, and the air was absorbed within ten days) It was now clear, however, that the infection was being overcome, and improvement continued until discharge on *Jan 1, 1958*



Treatment and course of illness

No *C albicans* could be grown from any source except the perianal skin lesion, which ultimately cleared up on treatment with 1% gentian violet

The course of the patient's illness and the treatment are shown graphically in the accompanying chart

Comments

Previous experience with fulminating influenza led us to expect a secondary staphylococcal infection with probable death within one to three days of admission, and the patient's recovery is in part due to the prevention of bacterial complication by early and adequate antibiotic therapy Bacteria, however, were superseded by *C albicans* and the extensive moniliasis which developed might well have proved equally fatal

We were much impressed with the speed with which *C albicans* disappeared from the sputum under treatment with nystatin, and believe that the inhalations were the decisive factor in this, because nystatin is little absorbed from the intestinal tract We have been unable to find any published report of the use of aerosol nystatin therapy in moniliasis The dosage used was arbitrary but appeared highly effective and caused no complications Possibly a smaller dose might have achieved the same result

ADDENDUM

Since the patient was discharged from hospital she has had a return of cough and sputum with evidence of a developing bronchiectasis at the left base, and monilia have been recovered from sputum obtained after postural coughing Her general condition is excellent and the fact that monilia were not completely eliminated in the acute stage does not affect our belief that the nystatin by aerosol played an important part in her survival Treatment is continuing with intensive physiotherapy and further nystatin inhalations with again a prompt disappearance of monilia from the sputum

We should like to thank Dr T B Williamson for the pathological reports and for his helpful comments on the case

PERFORATION OF DUODENAL DIVERTICULUM

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THREE types of duodenal diverticulum are described (1) those in the first part of the duodenum, which are pseudodiverticula associated with the scarring of peptic ulceration, (2) true congenital diverticula close to the ampulla of Vater and consisting of a pouch formed by the whole thickness of the duodenal wall, and (3) diverticula in the second and third parts of the duodenum, probably of the pulsion type and consisting of an extrusion of the mucosa and submucosa usually alongside a blood-vessel

The majority of duodenal diverticula cause no symptoms, they are usually wide-necked and their contents fluid, and therefore stagnation does not occur In some cases, however, symptoms are produced by pathological changes within the diverticulum or by mechanical pressure from it Ulceration with perforation or erosion of a large vessel, peridiverticulitis, malignant change, pressure on the biliary or pancreatic ducts, and calculus formation, occasionally with fistula, have been described (Chitambar 1953)

Mackay and Page (1955) reviewed eight cases and added a ninth case of perforation of a duodenal diverticulum

Case-report

On Feb 24, 1957, a woman, aged 67, was admitted to the surgical wards of Maryfield Hospital Six hours before admission she had been seized with a sudden knife-like pain in the right hypochondrium, associated with nausea but no vomiting The pain gradually spread to the whole of the right side of her abdomen She said she had undergone cholecystectomy in 1929, hysterectomy in 1933, appendicectomy in 1940, and two operations (nature unknown) for duodenal ulcer Recently she had enjoyed good health

On examination her general condition was good Temperature 97 8°F Pulse-rate 96 Blood-pressure 130/60 mm Hg She had tenderness and guarding on the right side of her abdomen, especially in the right hypochondrium, where a tender mass was palpable Bowel sounds were absent The mass was thought to be a tense inflamed gall-bladder, in spite of the history of cholecystectomy

Laparotomy under anæsthesia with thiopentone, gallamine, and nitrous oxide and oxygen was done through a right upper paramedian incision Numerous dense adhesions were found, especially around the duodenum The gall-bladder was present and healthy The appendix had been removed A satisfactory posterior gastro-enterostomy was present, together with a pseudodiverticulum opposite a healed duodenal ulcer On further exploration, after the separation of adhesions, a retroperitoneal cystic swelling was found lateral to the second part of the duodenum This swelling contained orange-coloured sebaceous material which was removed, exposing an opening into the duodenum on the medial side of the posterior wall, just distal to the ampulla of Vater This opening was closed with two catgut sutures A rubber-dam drain was brought out through a stab wound in the flank, and the abdomen was closed in layers

Microscopic examination of the edge of the opening in the duodenum showed infected gastro-intestinal mucosa containing bilestained debris and probably duodenal in origin

Postoperative recovery was delayed by drainage of bile-stained fluid in small quantities from the stab wound This cleared after three weeks, and the patient was discharged to a convalescent home

Follow-up.—A barium meal on March 23, 1957, showed a normally functioning gastro-enterostomy, but the duodenum could not be filled with barium Follow-through showed no leak of barium

Comment

Perforation of a duodenal diverticulum is rare Of the nine cases previously reported in the English literature (Mackay and Page 1955) only two were diagnosed pre-operatively, and three were diagnosed only at necropsy in spite of previous laparotomy Preoperative diagnosis is difficult not only because the condition *is rare but* also because the lesion is in an inaccessible situation These cases require early laparotomy, and *the retro*-peritoneal part of the duodenum should be carefully examined for a diverticulum

We wish to thank Mr W G Campbell for permission to publish this case, which was treated under his charge, and Dr M de G Gribble for the pathological report

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Preliminary Communication

HEPATIC VENO-OCCLUSIVE DISEASE

PRODUCED EXPERIMENTALLY IN RATS BY THE INJECTION OF MONOCROTALINE

FOR the past eight years the University College of the West Indies has made an intensive study of the various types of liver disease in that area

One of the diseases studied has been hepatic veno-occlusive disease,[1–3] which is not confined to humans in the West Indies but is found also in animals and has a world-wide distribution [4] The pathological findings consist of an intimal overgrowth of connective tissue of the hepatic veins, causing partial or complete occlusion centrilobularly, with a consequent damming back of the blood in the sinusoids, which become distended (the so-called " lagoons of blood ") The ultimate result is a generalised fibrosis of the liver, with a predominant centrilobular distribution

There is much evidence to show that the condition is caused by the pyrrolizidine group of alkaloids found in Compositæ (genus Senecio), the Leguminosæ (genus Crotalaria), and Boraginaceæ (genus Heliotropium) [5]

Considerable investigation has been carried out on the various diseases in animals caused by the ingestion of the above plants, such diseases are the walking disease of horses and cattle in Northwestern Nebraska,[6] *dunsiekte* or enzootic liver disease of equines in South Africa,[7] [8] walkabout disease in Northwestern Australia,[9] Winton disease of New Zealand,[9] and ragwort poisoning of horses and cattle in the United Kingdom.[10]

In the field animal and in the experimental animal, various lesions of the liver, other than veno-occlusive disease, have persistently been described, they are centrilobular congestion with " lagoons of blood ", hæmorrhagic necrosis, cirrhosis, the megalocytosis of Bull,[11] endothelial hyperplasia, and neoplasia [12]

Although hepatic veno-occlusive disease has been described in various field animals,[3–5] the pathological findings have not been described in the experimental animal except by Martin and Hill in horses suffering from the walking disease of Northwestern Nebraska [13] after feeding with *senecio riddelli*, and by Berry and Bras in a calf after feeding with *crotalaria fulva* [14]

At the Royal Free Hospital, one of us (C F S) has injected Wistar rats intraperitoneally with monocrotaline (91 7 mg per kg of body-weight) Monocrotaline ($C_{16}H_{23}O_6N$) is one of the pyrrolizidine group of alkaloids isolated from several species of Crotalaria (Leguminosæ) Within ten days hepatic veno-occlusive disease developed, with intimal thickening of the centrilobular veins causing partial or complete occlusion and lagoons of blood within the sinusoids in about a quarter of the animals The dosage of monocrotaline, the age of the rats, and the extent of the lesion appear to have no relationship, but further investigations are being made to establish the pathogenesis of the disease

We wish to thank Dr Roger Adams, of the University of Illinois, for the supply of monocrotaline

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Terminal Apnœa

AT a meeting of the section of anæsthetics, on Feb 20, Dr H J BRENNAN said that apnœa persisting at the end of operation must be regarded not as an entity but as a symptom of some underlying condition, the diagnosis of which was essential for the satisfactory treatment of the patient

It was important to distinguish between central and peripheral causes of the apnœa This might best be done by faradic stimulation of the ulnar nerve at the elbow If such stimulation resulted in full flexion and ulnar deviation of the hand, the apnœa was central in origin, if there was no response it was probably due to a residual effect of the relaxant drugs on the myoneural junctions In the latter event, especially if there was any question of hypokalæmia, it was most important that the anæsthetist should maintain pulmonary ventilation until the patient was breathing regularly—even if somewhat inadequately—on his own Then, and not until then, neostigmine should be administered, but this drug should never be given to a patient who was apnœic as a result of tubocurarine or gallamine

Central causes of persistent apnœa included carbon-dioxide depletion and carbon-dioxide excess, the latter either producing true carbon-dioxide narcosis in emphysematous subjects whose respiration had been controlled, or potentiating certain neuromuscular blocking agents The commonest central mechanism, however, was derangement, not depression, of the respiratory centre This could result from regular rhythmical ventilation of apnœic patients, especially if they were strongly vagotonic In the absence of any potent respiratory stimulus, this form of apnœa would persist almost indefinitely, but it could be terminated immediately by flexing the neck, or letting down the cuff of a cuffed tube, or stimulating the carina with a suction catheter

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" The first peculiarity of the career in pure research is its complete unpredictability In many forms of professional work a man can feel assured that a high degree of ability coupled with the capacity for hard work will eventually bring him to a satisfactory position in his chosen way of life In scientific research this is not so However good a scholastic and academic record a young man may have, neither he himself nor anybody else can predict that he will be a productive research worker, it is only by trying that he can find out whether he has the additional qualities of originality and flair on which success depends All basic research is a pioneering effort and the man who takes it up is embarking on an adventure, these facts accord ill with the security-mindedness that has become so much more prominent a characteristic of the people of this country in recent years "—SIR CHARLES HARINGTON, SC.D , F R.S , *Leadership in Scientific Research* London, 1958

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Reviews of Books

The Sanctity of Life and the Criminal Law

GLANVILLE WILLIAMS, PH D, fellow of Jesus College, Cambridge, formerly Quain professor of jurisprudence, University of London London Faber & Faber 1958 Pp 319 30s

THIS important book is derived from a course of lectures given at Columbia University It overelaborates, perhaps, on American practices, but Dr Williams has encompassed his subject from historical, moral, religious, and philosophical aspects as well as from social, medical, and legal ones, in a way possible only to the trained legal mind His approach is very radical, and, as theological beliefs are easy to assail on logical grounds and as religious doctrines have often blocked reform, the clergy (especially the Roman Catholic) are sharply criticised Some readers' lingering doubts about desirable change may be finally stilled, notably regarding abortion, to which, rather surprisingly, a third of the book is devoted He goes very much further than most in the liberty he would allow a mother in killing a child she considered defective, but in criticising the capriciousness of the infanticide law he is on firmer ground He argues in favour of contraception and sterilisation, but his views on the importance of a background of epilepsy or mental defect are not in proportion and outrun the opinions of many specialists Dr Williams' apparent advocacy of compulsory sterilisation might be harmfully taken much further by others than he himself intended His account of suicide [1] is clear and concise, yet quite comprehensive, and will be the standard summary of the subject until the law is changed There are also chapters on artificial insemination and euthanasia, but he does not attempt to tackle homicide Summaries at the end of chapters would have been helpful

The book is well and engagingly written and there is much to interest the medical reader, whatever his specialty It will, for example, be news to many that destruction of a deformed infant may be unpunishable in law on the ground that it is "not human" and that a person who permits removal of his teeth without adequate reason is technically guilty of a criminal offence The book carries the story up to the Bodkin Adams case and the Homicide Act of 1957

The understanding and practice of medicine is once more enriched by a specialist from "outside", although he has supplied grounds for bitter argument (to the Roman Catholic the book will be heresy from end to end) There is something of Huxley's *Brave New World* about Dr Williams' approach, which will strike some as slightly sad

Recent Advances in Urology

HOWARD G HANLEY, M D, F R C S, surgeon, St Peter's, St Paul's, and St Philip's Hospitals, London, and lecturer, Institute of Urology London J & A Churchill 1957 Pp 270 30s

SINCE not all urology is surgical, a physician, Dr A R Harrison, and a bacteriologist, Dr K F Anderson, have contributed to this book, and Mr T L Chapman, Mr J D Fergusson, and Mr D M Wallace make up Mr Hanley's team

The useful chapter on radiology of the urinary tract describes aortography, perirenal air insufflation, and the X-ray image intensifier Conservative renal surgery has advanced considerably in the past ten years, and we are glad to see a chapter on hydronephrosis and partial nephrectomy There is a well-reasoned assessment of the treatment of acute and chronic retention, and an account of the various forms of prostatectomy performed at present. The section on bladder tumours includes a workable scheme for their clinical and pathological staging The present-day treatment of bladder tumours with interstitial radiation, external therapy, and partial or total cystectomy is ably recorded Other subjects discussed include the chemotherapy of urinary-tract infections, prostatic cancer, genito-urinary tuberculosis, and the surgery of the adrenal glands

This balanced review of progress will appeal to urologists and general surgeons, and also to those working for higher examinations

Medical Teleology and Miscellaneous Subjects

F PARKES WEBER, M A, M D, F R C P London H K Lewis 1958 Pp 86 15s

"I BELIEVE", says Dr Parkes Weber, "that in pathology an ætiological explanation is more likely to prove correct, if teleological points of view have not been neglected in thinking it out" He has here collected many of his short essays, some reprinted from periodicals and others revised chapters from his earlier work *Some Thoughts of a Doctor*, and the teleological viewpoint is implicit in many of them For all who rejoice in his leisurely style and explorations of the less familiar lanes of medicine, Dr Parkes Weber's latest publication will be an important event

Anesthesia and Otolaryngology

DONALD F PROCTOR, M D, assistant professor of laryngology and otology, Johns Hopkins University School of Medicine Baltimore Williams & Wilkins London Baillière, Tindall, & Cox 1957 Pp 268 56s

THE title is a little deceptive, for only about half the contents are strictly related to anæsthesia for otolaryngological operations, while the rest is concerned with general considerations common to anæsthesia for all operations, and with subjects ranging from respiratory resuscitation to the treatment of asphyxia neonatorum Dr Proctor's own background may supply the linking thread, for after many years in otolaryngology he turned to anæsthesia and then back to his original specialty Understandably he found a particular interest in those problems in both specialties created by the concurrent use of the patient's airway His text is inclined to be discursive, and contains several statements (that general anæsthesia is never given for tracheotomy, for instance) that would not be widely accepted On the other hand, it gives a good picture of the range and application of anæsthetic techniques for otolaryngological operations, and of their special difficulties

From Sterility to Fertility

ELLIOT E PHILIPP, M B, F R C S, M R C O G London Thorsons *1957 Pp 120 10s 6d*

POPULAR exposition of medicine here takes on the subject of undesired childlessness it is a subject more suitable than some Fears are unlikely to be implanted, and practitioners, general and special, may well prefer patients who consult them on this matter to know something of likely causes and possible cures The book will give them enough about both, here and there perhaps too much Doubtless "an operation to cure a rupture, if badly performed, may result in damage to the vas" but is it helpful to say so in a book of this kind? Some readers will find it a sad sign of the times that the idea of a family doctor, exercising continuous care, able to instruct in small matters, to advise in great ones, and actually consulting with consultants, is conspicuously absent There is a judicious chapter on artificial insemination and an instructive one on adoption

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Emergencies and Sickness in the Home (Aberdeen G & W Fraser 1957 Pp 63 *6s 6d*)—Dr Winniefred M Gray's handbook for mothers on domestic first-aid and nursing is notable chiefly for some useful directions on the prevention of home accidents Apart from this, its contents are in line with those of other first-aid manuals, and it is rather less well produced than the manuals of the recognised first-aid organisations

The Fundamentals of X-ray and Radium Physics (2nd ed Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 327 63s)—Dr Joseph Selman's textbook is intended chiefly for student radiographers, though doctors beginning training in radiology will no doubt find it useful It begins with elementary mathematics, and considers the fundamentals of X-ray physics and radiographic technique In the new edition the main revision has been in the section on radiation protection

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[1] See *Lancet*, March 15 1958 p 571

THE LANCET

LONDON 22 MARCH 1958

Coronary-artery Disease

In the many recent papers on coronary-artery disease nothing has appeared which challenges the view that it is loosely associated with a disturbance in the transport of lipid in the blood The most easily demonstrable feature of this disturbance is a raised level of serum-cholesterol, and a big effort is being made to discover what determines the level of serum-cholesterol in health and also its relation to fats in the diet Because lipids are transported differently in other species, this has necessitated laborious experimentation on man[1-5] From the findings up to date, all observers would agree that most fat of animal origin will raise the serum-cholesterol (oils from marine animals are an exception) and that most fats of vegetable origin will lower it (coconut oil is an exception) There is little agreement, however, about the nature of the chemical groups in the fats responsible for these changes Whereas **Keys** et al.[3] hold that saturated acids specifically raise the cholesterol levels, **Ahrens** et al[1] regard the effect of dietary fats as a function of their iodine value the more unsaturated the fatty acids, the greater will be the lowering of the serum-cholesterol Neither of these groups, each of whom studied the effects of natural fats, found any evidence that the "essential fatty acids"—linolenic, linoleic, and arachidonic acids—have any specific lowering action On the other hand, **Horlick** and **Craig**[4] and **Kinsell** et al[6] showed that in some subjects such an action was seen on giving ethyl linoleate and linoleic acid in pure form. These experiments are very difficult to carry out, and, since none of the investigating groups has exactly repeated the conditions of another, the results are not necessarily contradictory or mutually exclusive. It may turn out that all are partially right and that the different fatty acids under certain circumstances specifically affect the serum-cholesterol level We should add that, though a raised serum-cholesterol is the most easily measured feature of the disturbance of lipid transport, it is not necessarily the most important as regards coronary-artery disease **Smith**[7] presents evidence that other components of the β-lipoproteins—notably a pre-β-lipid separated by paper electrophoresis or ultracentrifugation—are more closely related with myocardial infarction **Walker** et al[8] also find that different fractions of the lipoproteins react differently to changes in dietary fat

We know, too, that both ovarian and thyroid-gland hormones may profoundly affect the transport of lipids in the blood A dried thyroid extract produces a sustained fall in the raised levels of lipoproteins,[9] and triiodothyroacetic acid may lower the plasma-cholesterol and β-lipoprotein levels without raising the basal metabolic rate[10] In an attempt to bring together the nutritional, endocrine, and clinical findings, **Oliver** and **Boyd**[11] have produced a helpful diagram, which relates a disturbed endocrine function to a disturbed lipid metabolism (secondary to dietary excess) and both to clinical coronary disease

The object of epidemiological studies has been to ascertain whether there is a causal link between a high incidence of coronary-artery disease, high levels of serum-cholesterol, and high intakes of dietary fat A diagram[12] showing an association between myocardial mortality-rates and dietary fat in different countries has often been quoted, but critics can point to the inaccuracies of national figures both for mortality-rates of specific diseases and for dietary intakes Indeed similar charts have been drawn showing an apparent relation of deaths from coronary-artery disease with dietary intake of animal protein[13] and also with the number of radio and television licences[14] National statistics certainly indicate an association between coronary-artery disease and "a high standard of living"; but perhaps they are not sharp enough to dissect out the various components in a prosperous life that may contribute to mortality

Epidemiological studies on a smaller scale are scientifically more respectable For example, the social-medicine department of Birmingham University[15] has analysed the records kept by eleven general practitioners to show the incidence of coronary-artery disease in men aged 60–69 The prevalence of the disease seemed to be unrelated to the mental demands of the men's occupation (or their smoking habits), but fairly closely related to the *physical* demands, being highest for men in sedentary work This is in line with the pioneer work of **Morris** et al,[16] who in London found the morbidity from coronary-artery disease greater in bus-drivers than in bus-conductors They attributed the relative immunity of the conductors to the beneficial effect of the exercise involved in climbing the stairs to the upper deck. **Keys** et al[17] have also discussed the influence of physical activity on serum-cholesterol levels in racial groups in many parts of the world, but they conclude that it is much less than the influence of the diet.

Neither epidemiological studies nor investigations of the chemical and physical properties of the blood will suffice to elucidate the pathology of myocardial infarction The essential lesion is in the walls of the artery, and it must be explained in terms of the pathological anatomy or pathological physiology of this structure The sequence—atheromatous plaque thrombosis infarction—appears a logical order, and certainly it is often followed But **Branwood** and **Montgomery**,[18] who studied in detail 144 hearts from suspected or proven cases of coronary-artery disease, found thrombi associated with only 39 out of 61 recent infarcts, and not all of these were occlusive Occlusion by soft atheroma was present in 11 others In some hearts a thorough search showed no obvious occlusion to account for the infarction, but in all cases with infarction there was obvious coronary stenosis Clearly there are different ways in which coronary infarction may be brought about, and it is illogical to suppose that all should be attributable to *one* environmental stress or to *one* disturbance of lipid transport in the blood No doubt most of us are too easily attracted to generalisations, which are oversimplifications

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[1] Ahrens, E. H., Hirsch, J., Insull, W, Tsaltas, T T, Blomstrand, R., Peterson, M L. *Lancet*, 1957, i, 943

[2] Malmros H., Wigand G *ibid* 1957 ii 1

[3] Keys A, Anderson J T, Grande F *ibid* p 959

[4] Horlick, L., Craig B M *ibid*. p 566

[5] van Handel, E. Neumann, H, Bloem, T *ibid* 1957 i 245

[6] Kinsell L W, Michaels, G D, Friskey, R W., Splitter S *ibid* Feb 15 1958 p. 334

[7] Smith E B *ibid* 1957, ii 910

[8] Walker W J, Weiner N, Milch L J *Circulation*, 1957, 15, 31

[9] Strisower, B, Gofman J W, Galioni, E. F, Rubinger J H, Pouteau J, Guzvich, P *Lancet*, 1957, i, 120

[10] Oliver, M F, Boyd G S *ibid*. p 124

[11] Oliver, M. F, Boyd G S *ibid* 1956, ii 1273

[12] Keys, A *J Mt Sinai Hosp* 1953 20, 13

[13] Yerushalmy J, Hilleboe, H E. *N Y St J Med* 1957, 57, 2343

[14] Yudkin, J *Lancet*, 1957, ii, 155

[15] Brown R. G, Davidson L. A G, McKeown, T, Whitfield, A. G W *ibid* p 1073

[16] Morris, J N, Heady J A, Raffle P A B., Roberts, C G, Parks J W *ibid* 1953, ii 1053

[17] Keys A, Anderson, J T Aresu M, Biörck, G, Brock J F Bronte-Stewart, B, Fidanza, F, Keys M H. Malmros H. Poppi, A Posteli, T. Swahn B, Vecchio, A *J clin Invest*. 1956, 35 1173

Another aspect of the problem was presented by **Duguid**[19] when he showed that some of the intimal thickenings which characterise atherosclerosis were products of thrombi, Mural thrombi in the process of organisation become incorporated in the artery walls and form fibrous thickenings of the intima **Duguid** and **Robertson**,[20] considering the mechanical effects of this, point out that the arteries are elastic tubes, dilating and recoiling with each pulse-wave, and that the incorporation into their walls of fibrous thickenings, which are relatively inelastic, must interfere with these movements and lead to structural disorganisation To this they attribute the intimal hæmorrhages cited by **Paterson**,[21] **Winternitz** et al,[22] **Morgan**,[23] and others as important features of atheromatous plaques, and, like **Morgan**, they consider that the blood destruction taking place in these hæmorrhages, and in mural thrombi, may account for much of the cholesterol and other fatty debris seen in atherosclerosis

The question of how lipids enter the arterial wall has attracted attention recently **Goldberg** and **Morantz**[24] have devised an ingenious preparation in which the aorta of a young chick is perfused with a pulsating stream of lipid-enriched blood for periods up to two hours Lipid infiltration of the vessel wall appears in the form of discrete droplets, mostly less than 0 5μ in size, distributed more densely along the inner than the outer curvature of the vessel wall and extending in depth sometimes as far as the outer wall The droplets are mainly situated in and around the connective-tissue cells that lie between the elastic lamina In our last issue Dr **Rutstein** and his colleagues described how they have cultivated portions of the inner linings of human aortas in tissue culture Cells grow out which closely resemble fibroblasts, and, if cholesterol is present in the culture medium in sufficient concentrations, these cells take up lipid Because this intracellular lipid deposition is inhibited if linoleic acid is added to the medium, these observations may provide an important new link between the chemists and the pathologists Though it would clearly be premature to assume that either of the processes observed by **Goldberg** and **Morantz** or by **Rutstein** et al represents the mechanism by which lipids are deposited in the formation of an atheromatous plaque in man, each presents an interesting possibility and they are not mutually exclusive

In considering the morbid anatomy of coronary-artery disease, we always come back, however, to the cause of intravascular thrombosis Is the mechanism for maintaining the fluidity of the blood connected with the mechanism for clearing it of absorbed fats? As is brought out by recent reviews,[25] [26] two substances—heparin (very probably) and ethanolamine phosphatide (possibly)—have roles in both mechanisms, which might explain the association between a disturbance of lipid transport and an increased coagulability of the blood But, if the complex mechanisms of blood coagulation are important, so equally may be the similarly complex mechanisms of fibrinolysis, whereby the organism dissolves and removes small deposits of fibrin **Astrup**[27] points out that in the healthy organism fibrinolysis is in a dynamic equilibrium with the fibrin-depositing coagulation process, and each of these two processes is regulated by activating and inhibitory systems **Greig**'s observation[28] [29] that alimentary lipæmia inhibits fibrolysis is therefore of great interest He found that the inhibitory factor in lipæmic plasma is in the β-lipoprotein fraction and that the composition of the β-liprotein is of more significance than the quantity Here is another link with the lipid-clearing system of the blood

It is not difficult to see how alimentary lipæmia, by disturbing the equilibrium between coagulation processes and fibrinolysis, might lead to deposition of small thrombi on the arterial walls and so be an essential part of the pathogenesis of atheroma On the other hand, it is hard to see how it can be in any way responsible for the large thrombi so often found in myocardial infarction For alimentary lipæmia is closely associated in time with the intake of fat, levels of blood-lipids being usually at a maximum about two to three hours after a fatty meal and returning to normal in about six hours So far as we recall, no clinical observers have recorded any regular association between the onset of the symptoms of myocardial infarction and the ingestion of a large fatty meal two to four hours previously indeed it is almost certain that no such association exists Thus, though a high intake of fat may account for the development of atheroma, it does not so readily explain why infarction should suddenly supervene

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[18] Branwood A W, Montgomery, G L *Scot med J* 1956, i, 367

[19] Duguid J B *J Path Bact* 1946 58 207

[20] Duguid J B, Robertson W B *Lancet* 1957 i, 1205

[21] Paterson J C *Arch Path* 1936 22 313, *ibid* 1938 25 474

[22] Winternitz M C Thomas R M, Le Compte P M The Biology of Arteriosclerosis Baltimore 1938

[23] Morgan A D The Pathogenesis of Coronary Occlusion Oxford, 1956

[24] Goldberg, L, Morantz, D J *J Path Bact* 1957, 74, 1

[25] *Lancet*, 1956 ii, 930

[26] Robinson D S French J E *Quart J exp Physiol* 1957, 42, 151

[27] Astrup, T *Lancet*, 1956, ii 565

[28] Greig, H B W *ibid* p 16

[29] Greig, H B W, Runde L A *ibid* 1957, ii 461

On the practical side, there is so far no satisfactory evidence that the lowering of serum-cholesterol levels, either by diet or by other means, reduces the liability to myocardial infarction, and until such evidence is obtained there is no clear case for drastic measures, dietetic or otherwise, to reduce cholesterol levels We can agree with McMichael [30] that "strong emotional devotion to corn-oil diets" will do no good Nevertheless it is wise to repeat to many middle-aged people, whether or not they have had a myocardial infarct, that "men dig their graves with their teeth" In this country the average intake of dietary fat is high and getting higher, and one can reduce it substantially without becoming a crank, upsetting the normal routine of a family kitchen, or forgoing social engagements The serum-cholesterol level is likely to fall if one eats sparingly of butter, cream, and pastries, chooses only the lean portions of meat and bacon, and makes fried food a luxury rather than a regular daily feature of the diet Such moderation can do nothing but good On the larger question of public health, Dr Sinclair,[31] whose letter on essential fatty acids and idiopathic hypercalcæmia appears on p 639, may prove to be right in thinking it important to increase the content of linoleic and other essential fatty acids in national diets To this end the margarine industry could be pressed into service and the old battles with the millers renewed But at present the evidence that we suffer from widespread partial deficiency of essential fatty acids, and that this contributes to coronary-artery disease, is no more than suggestive Perhaps use of the new method of gas-liquid chromatography to analyse these substances [32] will lead to much more precise knowledge both of the amounts of essential fatty acids actually present in different diets and about their role in lipid transport It will be best to await this new knowledge before pressing any public-health measures, though the need for investigation is clear enough to be urgent

Perinatal Mortality

Entry into this world is attended by many hazards The process, unlike fœtal development, can be controlled to some extent, but the control exercised sometimes adds to the hazards Even healthy infants born punctually may face difficulties For instance, malpresentation or disproportion can delay birth sufficiently to cause anoxia, necessary manipulation may give rise to frank or concealed trauma, or uterine inertia or hypoactivity, especially after early rupture of the membranes, together with decreasing vascularity of the placenta may induce fœtal distress Fœtal distress may also arise from a hypertonic uterus which compresses placenta, cord, and infant Thus, even at term trauma and asphyxia of antepartum or intrapartum origin may give the infant a poor start The well-developed postmature infant also has its problems, it needs more oxygen than a small premature baby, but may receive less because the O_2 saturation of the placental blood is reduced after 40 weeks [1] Also, with its fully developed respiratory centre the postmature infant is more likely to react to hypoxia by respiratory efforts in utero, with the danger that pneumonia will later develop, especially if the membranes ruptured early Finally, a larger baby may entail a longer labour and again hypoxia There are, too, wholly unexplained stillbirths among postmature infants [2] But Bound et al [3] consider that the chief risk in postmaturity is intrapartum asphyxia arising from toxæmia, hypertension, and long labour, and that otherwise the chances are as good as for all non-premature deliveries, and Prof F J Browne [4] insists that "the risks to the child of so-called 'postmaturity'" are non-existent The dangers attending premature birth are manifold and may be divided into those due to maternal and those due to fœtal causes

Among the maternal causes toxæmia and hypertension are common, and prematurity is said to occur ten times more often in multiple than in single pregnancy [5] If an infant is successfully delivered of a toxæmic mother its chances of survival seem to be no less than those of a child from a non-toxæmic mother [3], its troubles are mostly in utero either from spasm of the uterine blood-vessels due to maternal hypertension or from maternal convulsions which deprive it of oxygenated blood still more seriously Nor must it be forgotten that treatment which is beneficial to the mother may harm the infant Where twins are concerned the second child is the more likely to suffer, since it is usually the smaller, has been longer in utero since rupture of the membranes, and is more liable to have been subjected to manipulation All these factors tend to result in trauma and hypoxia Another cause of fœtal hypoxia is placental hæmorrhage, this seems to be commoner in multiparæ [6] Cæsarean delivery might be thought to be admirable for the fœtus, but, even when the operation is performed under ideal circumstances and with unruptured membranes, unexplained respiratory difficulties may follow [7]

The risks of fœtal origin are mainly due to incomplete development—for instance, a partially organised respiratory centre or lung alveoli whose lining cells are still cubical

Clearly, both prematurity and postmaturity are undesirable, but in most instances we have no idea why an apparently normal infant should be born out of time, for that matter, we do not know why it is born at the right time, and more information about this is urgently needed

Apart from fœtal malformation, about the causes of which we know nothing of practical use, and birth trauma, which is sometimes avoidable, fœtal distress is the most important cause of perinatal mortality Treatment of this must fail if the distress and anoxia have lasted long enough to cause extensive capillary hæmorrhages in the central nervous system and the viscera In prevention care must be taken to avoid giving the mother analgesics and anæsthetics which jeopardise the life of the infant In labour no drug of this kind is both fully effective and fully safe, but some are reasonably satisfactory Roberts et al [8] found that pethidine caused a decrease of 10–15% in the newborn infant's minute volume, compared with groups where pethidine had not been used, and the respiratory depression

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30 McMichael, J *ibid* March 8, 1958, p 528
31 Sinclair, H M *ibid* 1956, i, 381
32 James, A T, Martin, A J P *Biochem J* 1956, 63, 141

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1 Walker J *J Obstet Gynæc, Brit Emp* 1954 61, 162
2 McKiddie J M *Amer J Obstet Gynec* 1949 58, 386
3 Bound, J P, Butler, N R, Spector, W G *Brit med J* 1956, ii, 1191, 1260
4 *Lancet* March 1, 1958, p 479
5 Donnelly, M M *Amer J Obstet Gynec* 1956, 72 998
6 Kiessler, A *Acta obstet gynec scand* 1955, 34, suppl 1
7 Donald I *Brit J Anæsth* 1957, 29, 553
8 Roberts, H, Kane, K M, Percival, N, Snow, P *Lancet*, 1957, i, 128

continued for some hours after birth. Surprisingly the depression was greatest when the pethidine had been given to the mother more than 3¼ hours before delivery—and this without the complication of anæsthesia.

The means of judging the intra-uterine fœtal condition are limited. All that can be done is to note the heart-rate and look out for the passage of meconium, but by the time meconium is passed the fœtus may be severely distressed. The obstetrician must try to ensure that at birth respiration is not only spontaneous but adequate. The first and obvious step is to ensure that the airway is clear and to prevent aspiration of anything but air. Possibly parturition in the natural squatting position may aid drainage of mucus, but in addition the traditional sucker or some more efficient machine must be used. **Donald**[6] recommends that the stomach too should be emptied—especially after cæsarean delivery, where it is likely to be full. Moreover, a full stomach inevitably embarrasses respiration. A newborn, and particularly a premature, infant has much to contend with; its bones and cartilages are so soft that inspiratory effort can make the thoracic wall concave, and the walls of its pulmonary alveoli are held together by virtue of their moisture so that they have to be forced open. The actual force used was measured by means of a trans-œsophageal manometer modified from one described by **Dornhorst** and **Leathart**.[9] With this system **Donald**[6] obtained recordings from 40 infants at or near the time of birth, including the first breaths and the first cry. These records show that initial swings of pressure of 40 cm. water are common, and that in vigorous crying the pressure may momentarily reach 90 cm. These are high pressures, even compared with forced breathing in an adult, and show the effort which must be made to overcome cohesion of the alveolar walls. It is not surprising that the immature infant is not always successful without help. Once the alveoli are thoroughly opened respiration becomes far less effortful. Radiographs show that in mature infants pulmonary expansion is well advanced in about two minutes after the first breath, and in a few more minutes patchy mottling gives place to a clear lung field, and air can be seen in the stomach and duodenum. In a healthy but immature infant the process takes longer, and expansion is not complete in two hours. Radiography can be an invaluable aid in diagnosis and prognosis, but, remembering the work of **Stewart** et al.,[10] radiographs should not be taken needlessly.

Having begun to breathe, some infants fail; the causes may include the development of hyaline membrane, secondary atelectasis, or intracranial damage. Regarding hyaline membrane the only certain facts are that it is very rare in postmature infants, that it can develop after an apparently satisfactory cæsarean delivery, and that it by no means inevitably follows aspiration of liquor amnii and meconium by a severely asphyxiated infant, especially if it is postmature. Nor is recovery impossible from a syndrome suggesting hyaline membrane. The urgent requirement of every newborn child is for air and plenty of it, so that the lungs expand well, hypoxia is relieved, and the central and peripheral circulations carry well-oxygenated blood to all regions to ensure prompt reflex adjustments from an intrauterine to an intramundane existence. With a good start primary pulmonary trouble becomes increasingly improbable after twelve hours of life. Anything which will give the child this good start is worth trying, and for severely hypoxic and premature infants some sort of respirator is often essential. A mask or catheter pattern can be applied more quickly and easily than a tank type requiring a seal. The augmented-respiration method developed by **Donald**[6] has much to recommend it. The concentration and duration of oxygen administration have to be carefully determined, in order to avoid the disaster of retrolental fibroplasia.[11] But whatever the perfection of the machine and the skill of the operators there will still be failures. Sometimes the cause is unsuspected cerebral damage incompatible with life; it is often impossible to distinguish between a primary pulmonary condition, birth trauma, pneumonia, and intraventricular hæmorrhage.

Our ignorance of perinatal mortality is still appallingly extensive, and we hope that the important national survey by the National Birthday Trust Fund[12] will show how we can reduce it. Meanwhile the number of deaths can be curtailed only by unfailing vigilance and the wholehearted cooperation of all who attend women in pregnancy and labour.

The Pyramidal Tract

The clinical neurologist pictures the pyramidal tract as the main corticofugal pathway from the motor cortex to the pons, medulla, and spinal cord, and as the highway for impulses subserving voluntary movement, with an additional inhibitory effect on lower motor centres by which muscle tone is controlled. The pyramidal syndrome—weakness without muscle-wasting, increased tendon-reflexes, absent abdominal reflexes, and extensor plantar responses—is taken to indicate a lesion of this tract. This view is in part demonstrably inaccurate, and **Bucy**[13] suggests that the concept of the pyramidal tract has neither structural nor functional validity and should be abandoned.

Holmes and **Page May**[14] in 1909 concluded, from a study of retrograde degeneration in lesions of the cervical cord in man and animals, that the great majority of the tract was derived from Betz cells in the precentral convolution. This is still commonly taught (though not by **Holmes**), even though for over twenty years evidence from the correlation of fibre and cell counts has shown that only a small proportion of the fibres can be derived from Betz cells. Degeneration studies suggest that some come from the parietal cortex, but the origin of over two-fifths of them is still unknown. It is not established that these cells are exclusively of cortical origin, and it has even been questioned whether all the fibres are descending.

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[9] Dornhorst, A. C., Leathart, G. L. *ibid.* 1952, ii, 109.

[10] Stewart, A., Webb, J., Giles, D., Hewitt, D. *ibid.* 1956, ii, 447.

[11] Kinsey, V. E. *Arch. Ophthal., N.Y.* 1956, 56, 481.

[12] See *Lancet*, March 1, 1958, p. 469.

[13] Bucy, P. C. *Brain*, 1957, 80, 376.

[14] Holmes, G., May, W. P. *ibid.* 1909, 32, 1.

On the functional side also, inroads have been made into the concept of the pyramidal tract as the sole pathway for voluntary movements In monkeys section of the medullary pyramids produces by no means complete loss of voluntary movement, and extirpation of the precentral cortex causes a weakness which is not particularly spastic and in which muscle wasting occurs In man, too, limited precentral cortical ablations may give rise to weakness with wasting and little spasticity, nor are the abdominal reflexes abolished Such observations (many of them made by Professor BUCY and his school) have been known for some years Even more interesting information has come from operations, used in the treatment of parkinsonism and allied conditions, in which the peduncular tract is cut In such cases cutting the central portion of the peduncles, in which the *majority* of the precentral corticospinal fibres lie reduces tremor and involuntary movement, often greatly, but voluntary movement, even finely coordinated and controlled, may be little changed, and spasticity and increase in tendon-reflexes are inconspicuous The plantar response does, however, tend to become extensor —a change also noted after extirpation of the precentral cortex in man All that seems to be left of the pyramidal syndrome is the Babinski response, and even this is being called in question From time to time cases are cited in which the pyramidal tracts are demonstrably intact histologically yet the Babinski response is present This is usually explained by postulating a functional lesion in the tracts—a reasonable explanation because reversible loss of function in the anatomically intact tract is known to occur in various toxic states and in epilepsy NATHAN and SMITH[15] carefully studied two cases in which the pyramidal tract was undoubtedly sectioned and yet the plantar responses remained flexor for many weeks This is more difficult to explain If the sign of Babinski is not present when the tract has been completely interrupted, then this can no longer be accepted as the clinical sign par excellence of a pyramidal lesion The evidence on this point is still too incomplete for final judgment

These facts seem to justify BUCY's strictures on the "pyramidal system" as an "old erroneous idea" embodied in "old antiquated terminology" To some extent he is tilting at a windmill Most neurologists have long accepted a radical revision in the exact site of origin of the pyramidal tract and have modified their view of it as the sole transmitter of voluntary movement They retain, however, some regard for spastic weakness and upgoing toes as signs of interruption of the main corticospinal tract—even while admitting that these signs are not invariably found How far even this is justified is debatable Such doubts have not yet found their way into standard textbooks—general medical texts offending more in this respect than neurological—and the mummified tradition they sometimes reflect should not be mistaken for living opinion Professor BUCY does us a service in drawing attention to the discrepancy

Annotations

AGAINST THE COMMON COLD

AMONG the diseases due to microbial infection, the common cold has held out most strongly against either elimination or control The apparently trivial but practically important differences between the virus strains make it the most elusive of diseases The "tame" virus carefully maintained in the Common Cold Research Unit's laboratories had little of the dramatic effect of the "wild" variety imported into a group of scientists after a period of isolation from the rest of mankind had made them relatively susceptible[1] The history of trials of vaccines against apparently more stable and specific forms of respiratory pathogens such as the influenza virus shows that, as in the recent experience with "Asian" influenza, success follows only when the vaccine is specific to the current epidemic strain The common cold cannot be dismissed as a mere nuisance, for it is too commonly the precursor of more serious infection and even death in patients already crippled by chronic respiratory disease Any novel approach to the problem, however unpromising it may appear, is therefore to be regarded with hope and interest

In this issue we publish two articles by Dr J M Ritchie on cognate aspects of the prevention or modification of the effects of secondary bacterial invasion by organisms normally saprophytic in the oropharynx The notion common to both reports is an acceptance of the present impracticability of matching vaccine to epidemic virus and the need either to prevent secondary invasion or to abort it Dr Ritchie describes how his own early disbelief has had to give way against evidence from the small but carefully controlled trials he has conducted first of vaccines prepared from the flora of the subject's own pharynx and then of antibiotics to which these organisms were shown to be sensitive by the curtailment or suppression of the more distressing symptoms of the common cold

In a disease as protean as the common cold, the conduct of controlled trials is always difficult The subjective nature of the clinical assessment demands very strict control of psychological factors, and anecdotes of entreaties for revaccination from people who had received dummy preparations in previous trials emphasises this need In this instance it has been met by random allocation of volunteers to groups given either autogenous vaccine or saline and the independent assessment of patients' reports by medical staff ignorant of these allocations

Since these autogenous vaccines could not be expected to prevent the initial virus infection, the incidence of mild prodromal upsets should not be very different in the vaccinated and control series, and for the first two months of the trial this was the case On the other hand, the proportion of all obvious infections which developed into distressing full-blown colds was much lower in the vaccinated groups After the second month of the trial, administrative and other difficulties entailed the withdrawal from the continuing source of infections of some of the initial group of volunteers in both series These men do not seem to be very obviously self-selected, and their subsequent experience does not suggest that they had an inherently better resistance to disease Indeed, those who persevered might have had the incentive of a worse cold history in the past, but they had fewer colds than those who did not complete the vaccination course. They also had relatively less absence from work because of colds and other respiratory-tract infections than did the remainder of the vaccinated subjects and much less than those who had received physiological saline solution.

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[15] Nathan, P W , Smith, M C *J Neurol Neurosurg Psychiat* 1955, 18, 250

[1] Andrewes, C H Lovelock, J E , Sommerville T *Lancet*, 1951, i, 25

Ritchie's second experiment compared the experience of volunteers randomly divided into four groups. As soon as they felt a cold was beginning, three of these groups were given oral antibiotics to which their own mouth organisms were sensitive, the others received inactive tablets. Independent assessment of the respiratory infections suffered in the following winter showed that, while the incidence of insipient colds reported was similar, only 7% of those in the antibiotic-treated group went on to full development compared with 48% among the control series.

Although it is always possible for the scientific purist to suggest inadequacies in experimental design or method, the care with which these small studies have been conducted combines with the consistency of the results obtained to suggest that the underlying thesis merits more extensive trial. Although such a trial might be carried out on a volunteer population drawn, like the present one, largely from relatively healthy workers in industry, the application of the methods involved would be particularly apposite in patients with chronic respiratory disease. The widespread use of antibiotics may carry the epidemiological risks involved in building up resistant strains. But in chronic bronchitics, where repeated serious infections hasten deterioration and death, there would be a useful place for this *via media* between continuous antibiotic medication and a policy of masterly inactivity.

THE IMAGINARY TEXTBOOK

UNDER the title *La Musée Imaginaire*, André Malraux has written of those advances in pictorial reproduction that have made possible an abundance of art books of high standard, enabling us to enjoy in our homes fine pictures from the world's museums. The converse is a well-known feature of medical London, where the Wellcome Museum of Medical Science (183, Euston Road, London, N.W.1) is virtually a textbook on walls. Here 10,000 visitors a year inspect the displays, which are very well produced and laid out. As when it was founded in 1914, the museum is again devoted to diseases found in tropical countries, in each case there is a written account of ætiology, diagnosis, prevention, and treatment, prepared by experts or with their assistance, with lavish illustrations—photographs, drawings, diagrams, photomicrographs, models, and specimens. There is one living exhibit—a tank of Gambusia fish, which eat mosquito larvæ and provide a cheap tool in malaria control.

The emphasis of the exhibition changes with that of the branch of medicine it reflects. Prevention is becoming more prominent in every section. The displays dealing with syphilis and plague are much smaller than they used to be, and syphilis is included among the other spirochætal diseases. The section on tuberculosis is expanding at the expense of that on leprosy, and the common cold and measles find a place. 48 panels are devoted to malaria and 33 to nutrition and malnutrition, no doubt these proportions will be reversed as the malaria-eradication campaign progresses, unless more energy is put into correlating food-production and world population

Students of tropical and general medicine and pathology should find much to interest them here, and excellent conditions for study, and the "twenty questions" section will provide a stimulating, if humiliating, test of what they have learnt.

TWO NEW SULPHONAMIDES

THE introduction of sulphonamide compounds for the treatment of bacterial infections by Domagk in 1935 marked the beginning of a new epoch in therapeutics. Their effectiveness encouraged the search for other agents suitable for the treatment of infections, and in due course penicillin and other antibiotics were discovered. These developments tended to overshadow the sulphonamides, though these are still widely used and there has been continuous progress in the introduction of new compounds. It was fitting that a recent conference in New York largely devoted to new sulphonamides should be opened by Domagk with a review of progress during the past twenty-five years.[1]

Two products—sulphachloropyridazine and sulphamethoxypyridazine—have attracted particular attention. Structurally they differ only slightly, the first is 3-sulphanilamido-6-chloro-pyridazine, and the second the corresponding 6-methoxy derivative. They both have high antibacterial activity, quantitatively and qualitatively similar to that of sulphadiazine and greater than that of sulphadimidine and sulphisoxazole.[2 3] But there are some striking differences in their metabolism in the body, which greatly affect their administration and use in clinical practice.

Sulphamethoxypyridazine is well absorbed after oral administration and diffuses freely into the body-fluids, particularly into the cerebrospinal fluid.[4] These properties are shared by many sulphonamides, but *sulphamethoxypyridazine is exceptional in the slow excretion of its free form in the urine.* As a result it provides higher and more sustained levels in the plasma than any other therapeutically effective antibacterial sulphonamide.[5–11] The conjugated form is excreted much more rapidly through the kidneys, so that in the plasma most is present in the free state. Both forms are highly soluble in the urine.[3 5] In freshly drawn oxalated human blood, nearly all of the drug is in the plasma and little or none is found in the red cells.[10 11] Therefore, levels in whole blood are, on the average, only about 60% of the corresponding levels in the plasma. After a single oral dose of 0.5–4.0 g., peak concentrations are reached in about three hours, and are sustained for a further three or four hours.[12] Thereafter the concentration declines slowly and the time taken for a fall to half the peak value is about fifty-five hours.[9] A similar time is taken for the excretion in the urine of half the administered dose. In these circumstances the drug readily accumulates in the body. When a dose of 1.0 g. is given every forty-eight hours, a slight cumu-

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1 Domagk, G. *Ann. N.Y. Acad. Sci.* 1957, 69, 390.
2 Neipp, L., Mayer, R. L. *ibid.* p. 449.
3 Litchfield, J. T. *Int. Physiol. Congr.*, Brussels, 1956.
4 Boger, W. P., Strickland, C. S., Gyle, J. M. *Antibiot. Med.* 1956, 3, 378.
5 Roepke, R. R., Maren, T. H., Mayer, E. *Ann. N.Y. Acad. Sci.* 1957, 69, 457.
6 Foerster, D. K., Martin, W. J., McGuckin, W. F., Nichols, D. R. *Proc. Mayo Clin.* 1956, 31, 678.
7 Frisk, A. R., Wassen, A. Antibiotic Annual 1956–57 (edited by H. Welch and F. Marti-Ibanez) p. 424. London.
8 Jackson, G. G., Grieble, H. G. *Ann. N.Y. Acad. Sci.* 1957, 69, 493.
9 Jones, W. F., Finland, M. *ibid.* p. 473.
10 Nichols, R. L., Finland, M. *J. Lab. clin. Med.* 1957, 49, 410.
11 Nichols, R. L., Jones, W. F., Jr., Finland, M. *Proc. Soc. exp. Biol., N.Y.* 1956, 92, 637.
12 Finland, M., Jones, W. F., Jr., Ziai, M., Chernick, G. R. *Amer. J. med. Sci.* 1957, 234, 505.

lative effect is shown by the concentrations in the plasma over several days [10]

A long-acting sulphonamide has some advantages in both prophylactic and therapeutic use Only one dose a day is needed, and in the treatment of most susceptible infections an initial dose of 1 0 g followed by 0 5 g every twenty-four hours is sufficient [12] When high sustained blood-levels are required to eliminate more resistant organisms, an initial dose of 2 0 g followed by 1 0 g daily may be given In the prophylaxis of streptococcal infections a weekly dose of 30 mg per kg of body-weight has been used (about 1 5–2 0 g in an adolescent or young adult), and has been found satisfactory in a preliminary trial [13] As the drug so readily accumulates in the body it is advisable to determine the blood-level periodically if long courses are given, especially if renal function is impaired

The other compound, sulphachloropyridazine, shows numerous metabolic differences After a single oral dose the chloro derivative has a half-life in the plasma about a fifth as long as that of the methoxy derivative Urinary excretion is much more rapid with the chloro derivative, and the time taken for elimination of half the dose in the urine is only about a seventh of that for the methoxy compound [8] As a result, higher and more frequent dosage —usually about 0 5–1 0 g thrice daily—is needed with sulphachloropyridazine to attain adequate blood-levels On the other hand, urinary levels are higher, and a smaller proportion is present in the conjugated form This drug may therefore be useful in the treatment of urinary-tract infections [14], but in pyelonephritis high plasma and tissue concentrations may be more important than the level in the urine, which does not come into contact with the more deeply seated lesions On this basis, sulphamethoxypyridazine has been used to produce high, sustained blood-levels for the treatment of urinary-tract infections, and satisfactory results have been obtained [15]

The investigations so far on these two sulphonamidopyridazine derivatives show that they are among the most active sulphonamides They are clinically well tolerated Their toxicity is probably similar to that of other antibacterial sulphonamides in current use, though this can be fully established only by longer clinical trials These two compounds, so closely related chemically, have some sharply differing biological properties which will greatly influence their therapeutic applications

RESEARCH ON POPULATION GENETICS

THE Medical Research Council began to take an active part in developing research in genetics over twenty years ago With the advent of nuclear energy this activity was increased, and the Council is seeking to recruit additional workers for research in university departments or as members of its own scientific staff [16] The Council itself has lately made two important moves first, the formation in London of a Clinical Genetics Research unit under the direction of Dr J A Fraser Roberts, which began work last April, and now the establishment at Oxford of a complementary Population Genetics Research Unit under the direction of Dr A C Stevenson, formerly professor of social and preventive medicine at the Queen's University of Belfast

Hypotheses on the genetical structure of human populations are derived largely from theoretical considerations or from observations on experimental populations of animals, and the new unit will seek to test the validity of these in man The unit's work will probably include studies of the frequencies and patterns of marker traits in the population and of genetical linkage, and possibly studies of fertility patterns and of selection factors in marriages The unit is to be accommodated at the Warneford Hospital and will in addition have offices in Oxford If there is a local demand, genetical counselling clinics may be established at various centres

LUNG RESECTION FOR BRONCHIECTASIS

A YEAR or two ago we drew attention to the favourable results of conservative management of bronchiectasis and suggested that surgical treatment is rarely desirable, because of the relatively high incidence even in experienced hands of postoperative complications such as pulmonary collapse, and because of the considerable risk of further bronchiectasis in the remaining lung [1] A follow-up study by Gudbjerg [2] of Copenhagen illustrates these points afresh

52 patients treated by dissection lobectomy or segmental resection for unilateral disease were re-examined bronchographically after an average interval of five years 2 patients had died in the immediate postoperative period, and 4 more during the follow-up, and in this potentially most favourable group only half were cured in the sense of having no remaining bronchiectasis demonstrable radiologically (Nothing is said about pulmonary function in these patients) In a third, fresh bronchiectasis was found to have developed, and the remainder had not had a radical operation The results were better for right-sided operations, especially if confined to the middle lobe Operations on the left lung were often unsatisfactory, particularly if the lingula was conserved after a lower lobectomy As would be expected, postoperative pulmonary collapse or empyema increased the risk of a bad result, and so did increasing age In a small group with unilateral disease submitted to pneumonectomy, the mortality was prohibitive, and half the patients died within four months Of 32 patients with bilateral disease 5 died soon after operation and a further 8 during follow-up, all but 2 survivors showed extension of the disease

By the criteria of the death-rate and radiological findings these results are discouraging, and knowledge of the functional capacity of those who were "cured" might make the picture still more sombre There are probably several reasons The incidence of postoperative complications was considerable, and the average age was very high, the series included people in their fifties and sixties who would not be operated on nowadays It is true that antibiotics, physiotherapy, anæsthesia, and surgical technique have all improved since these patients had their operations, but improved technique is unlikely to affect the most important factor—namely, the inevitable distortion of the bronchial tree and interference with the drainage of the remaining bronchi Gudbjerg suggests that there may be a further factor—constitutional susceptibility to bronchial infection

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THE death has been announced of SIR THOMAS WILSON, consultant gynæcologist to Adelaide Hospital

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[13] Lepper M H, Simon A J, Marienfeld C J *Ann N Y Acad Sci* 1957, 69 435

[14] Nanda K G S Batterman R C *ibid* p 521

[15] Harris A P, Riley, H D, Jr Knight V *Arch intern. Med* 1957, 100 701

[16] Report of the Medical Research Council for the Year 1955-56, p 9 H.M Stationery Office, 1957

[1] *Lancet* 1955, ii 489

[2] Gudbjerg, C E *Acta radiol., Stockh*, 1957, suppl 143

Public Health

TUBERCULOSIS CASE-FINDING BY MASS RADIOGRAPHY

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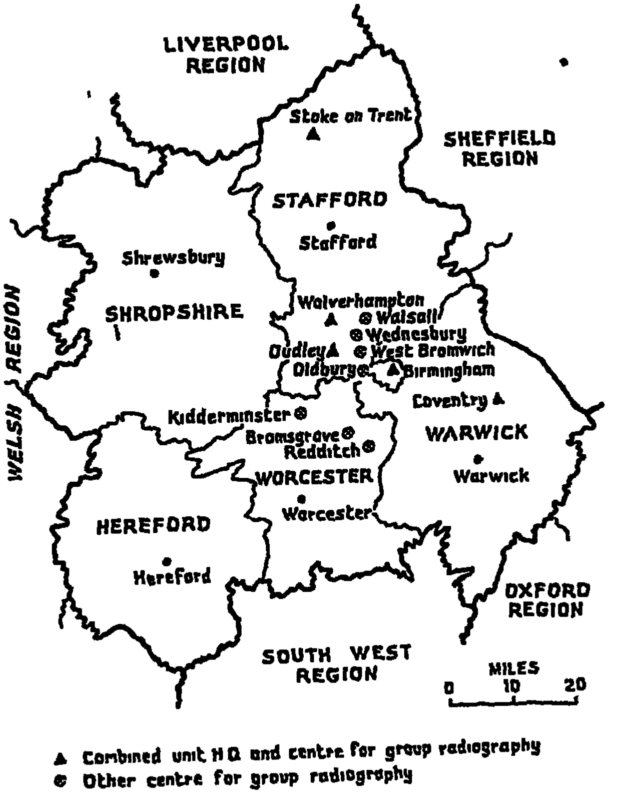
Since civilian mass radiography was introduced in this country in 1943, many and varied suggestions have been made for using it more profitably The ideas put forward have been good theoretically, but most of them prove difficult to put into practice using the present mass-radiography organisation and cumbersome equipment If there have been many suggestions and ideas, there has certainly been no dearth of reports on mass-radiography surveys In fact, where there is a clearly defined group of persons, the probability is that they have been X-rayed by mass radiography and the results have been reported

This article, therefore, will present nothing new and will not describe any unique method of using mass radiography It has been written simply to explain how mass radiography has been developed in one hospital region, and to show the extent to which it has contributed towards tuberculosis case-finding This development has followed a definite policy, which was decided on when I was appointed in 1951 Whether, up to now, it has succeeded or failed must be left to readers to judge and time to decide At least a standard of achievement is presented against which others, with the same resourc measure their own efforts



Development and Policy

The Birmingham hospital region has a popul about 4$^{1}/_{2}$ million This population is very u distributed There are densely populated areas around Birmingham, in the Black Country, C and Stoke On the other hand, large areas of Sh and Herefordshire are sparsely populated, and gre of Staffordshire, Worcestershire, and Warwicks rural

When the hospital board began to develop the the problem was to place the units strategically evolve a profitable policy governing their use It remembered that five or six years ago the downwa in the incidence of respiratory tuberculosis was apparent In view of this and the experience countries, it was clear that the time was comin routine mass radiography of factory employees general public, by themselves, would no lo economical In 1951 the regional advisory comm tuberculosis services recommended that mass-radi units should examine, as priorities, patients refe general practitioners, contacts, persons exposed risk of developing chronic respiratory diseases, an persons between the ages of 18 and 25 They als that they did not think it profitable to carry out r examination of employees in large concerns, exce entrants

Having made these two pronouncements, which pated the Medical Research Council (1953) re almost three years, the committee left the rest of th governing the detailed use of the units to the co adviser and the individual medical directors The mendations were accepted by the regional hospital and in order to implement them it was decided t up a service which would concentrate its main ef the thickly populated industrial areas but could a adequate mass-radiography "cover" to the rest region

This was achieved by establishing unit headq in the main industrial centres The buildings use adapted so that it was possible to use the standard apparatus with which the units were equipped, removing it from the van Hence units had base quarters to which they could return, at regular in to examine priority groups gathered from the surro industrial districts Between these visits they surveys elsewhere in the area allocated to them

On the inception of the National Health Servic were three units—Birmingham, Coventry, and hampton By 1951 the Birmingham unit had static, to deal with general practitioners' referr other fixed commitments The other two unit mobile roles In the next three years four unit added The deployment and character of work units at the end of 1956 are shown in table I T units outside Birmingham were mobile and retu base at regular intervals to carry out group surve

Birmingham, by its size and population, jus static unit Also in Birmingham and district we mobile units (one with greatly reduced staff) whic industrial and public surveys and gave a regular for group radiography in the Black Country Th

TABLE I—MASS-RADIOGRAPHY UNITS IN BIRMINGHAM REGION, 1956, SHOWING DEPLOYMENT AND WORK UNDERTAKEN

Unit	Area for mass-radiography surveys (population in parentheses)	Centres for group radiography*
Birmingham Static (Dr L. A. McDowell)	Birmingham and adjoining districts (1,200 000)	Birmingham (daily, Monday–Friday)
Birmingham Mobile Units A and B (Dr G P Bardsley)	Birmingham, Smethwick, Walsall, West Bromwich, Sutton Coldfield, Oldbury, and adjoining districts (1,618,000)	Walsall West Bromwich Wednesbury Oldbury } twice a month
Coventry Unit (Dr A G Evans)	Coventry and Warwickshire (756 000)	Coventry (monthly)
Dudley Unit (Dr R. J Posner)	Dudley, Worcester, Worcestershire, Herefordshire, part of Staffordshire (735,000)	Dudley (twice a month) Bromsgrove Redditch Kidderminster } monthly
Stoke Unit (Dr E Posner)	Stoke, Burton, North Staffordshire, North Shropshire (720 000)	Stoke (monthly)
Wolverhampton Unit (Dr J T Hutchison)	Wolverhampton, South Staffordshire, South Shropshire (718,000)	Wolverhampton (weekly)

* Groups X-rayed included general practitioners' referrals, antenatal patients, National Service recruits, self-referred persons, schoolchildren, contacts, miscellaneous groups including teachers and persons in contact with children

use was somewhat unusual, in that a tour was made visiting four centres in the Black Country twice a month At one of these centres the 70 mm equipment of the chest clinic was used

Tuberculosis Discovered

In this part the description of the results of the mass-radiography service will be restricted to active respiratory tuberculosis, because the discovery of the active case was the principal target during the five years reviewed An active case of tuberculosis, in this context, was one classified by the clinic or the hospital physician as requiring immediate treatment or close clinic supervision

The development of the service since 1952 and the results obtained are given in table II

Several points in this table are worth noting Firstly, the prevalence of active tuberculosis for the region as a whole has remained steady over the past three years This is contrary to what has been found in many other regions, where a fall to between 1 and 2 active cases per 1000 has been commonly reported In the second place, it will be seen that a static unit has a great advantage over a mobile unit, so far as discovery-rate is concerned The Birmingham static unit claimed about a third of all the active cases found in the region A mobile unit working in the same city, doing routine surveys of the general public and factory employees, was accordingly at a disadvantage and found very few cases Most of the other units which combined static group radiography with mobile mass radiography brought in a satisfactory yield of active cases The Birmingham B Unit which, as described, made a regular tour of centres in the Black Country, returned the high prevalence-rate of 5 active cases per 1000 Although the total number of persons examined by this unit in 1956 was small (16,854), it is confidently expected that there will be a steady increase as the value of the service becomes appreciated locally

General Practitioners' Referrals

It is now well recognised that group radiography of patients referred by general practitioners is one of the most profitable ways of using mass radiography This fact is shown quite strikingly in table III

For example, over the past five years, although patients referred by doctors represented only 10% of all persons X-rayed, 40% of all the active cases came from this group The prevalence in this group fell steadily as the general practitioners made increasing use of the facilities offered The prevalence, which was 22 9 per 1000 in 1952, fell by 45% to 12 5 per 1000 in 1956, while the number of patients examined increased during the five years by 260% The prevalence-rates for the middle years are comparable with the 20 per 1000 of Nash et al (1953), 22 per 1000 of Barr and Ritchie (1955), and the 16 per 1000 of Brett et al (1956), which they found among a comparable group of patients Sutherland (1952) recorded a figure of 28 per 1000 among 5702 patients examined during the first year of sessions for doctors' patients in Birmingham

TABLE III—ACTIVE CASES OF TUBERCULOSIS FOUND

Year	General practitioners' referrals			All other groups		
	No examined	Active cases	Prevalence per 1000	No examined	Active cases	Prevalence per 1000
1952	14,164	324	22·9	181,513	801	4 4
1953	26,125	513	19 6	297,194	874	2·9
1954	31,294	489	15 6	364,033	868	2 4
1955	39,886	551	13 8	326,240	678	2 1
1956	50,859	634	12 5	300,455	586	1·9

Patients Known to be Tuberculous Before Mass-radiography Examination

It has been suggested that the high proportion of active cases picked up by mass radiography may be attributed to the attendance of persons previously known to be tuberculous In the two years for which information on this point was available, only 5 8% (72) of the active cases in 1955 were previously known The corresponding figure for 1956 was 4 9% (60) Thus 95% of the active cases brought to light by mass radiography had not been diagnosed previously

TABLE II—NUMBERS EXAMINED AND PREVALENCE OF ACTIVE* TUBERCULOSIS FOUND BY MASS-RADIOGRAPHY UNITS OF BIRMINGHAM REGION 1952–56

Unit	1952			1953			1954			1955			1956		
	No examined	Active tuberculosis	Prevalence per 1000	No examined	Active tuberculosis	Prevalence per 1000	No examined	Active tuberculosis	Prevalence per 1000	No examined	Active tuberculosis	Prevalence per 1000	No examined	Active tuberculosis	Prevalence per 1000
Birmingham Centre	55,728	416	7 5	62,355	475	7·6	65,274	417	6 4	63,431	463	7 3	66,268	459	6·9
Coventry	45 469	295	6 5	54,074	259	4 8	57,694	205	3·6	50 805	114	2 2	52,682	115	2 2
Wolverhampton	54 148	238	4·4	62,986	242	3 8	53,919	192	3 6	53,810	177	3 3	54,599	177	3 2
Stoke-on-Trent (from June 27 1952)	21,843	124	5 7	65 424	235	3·6	69 076	258	3 7	54 120	196	3·6	70 660	221	3 1
Birmingham Mobile A (from July 1, 1952)	18 489	52	2 8	56,550	125	2 2	86,552	106	1 2	64,140	99	1 5	46,625	60	1 3
Dudley (from Aug 21 1953)				21 930	51	2 3	61 175	178	2·9	61,503	116	1·9	43 626	103	2 3
Birmingham Mobile B (from Dec. 14 1954)							1637	1	0·6	18,317	64	3·5	16,854	85	5·0
Totals	195,677	1125	5 7	323,319	1387	4 3	395,327	1357	3·4	366 126	1229	3·4	351,314	1220	3 5

* An active case of tuberculosis is defined as one requiring immediate treatment or close supervision at a hospital or clinic.

TABLE IV—NUMBER OF PERSONS EXAMINED AND ACTIVE TUBERCULOSIS DISCOVERED BY MASS RADIOGRAPHY IN THE HOSPITAL BOARD REGIONS OF ENGLAND AND WALES, 1956

Region	Population	Respiratory tuberculosis		Mass-radiography results			
		Notified cases	Incidence per 100,000	Units operating	Persons radiographed	Active tuberculosis	Prevalence per 1000
Newcastle	2,911,922	2729	94	6	179,694	864	4 8
Leeds	3,057,880	1855	61	3	165,845	268	1 6
Sheffield	4,189,470	2507	60	7	356,831	714	2 0
East Anglian	1,473,670	604	41	2	108,930	118	1 1
N W Metropolitan	3,908,540	3231	83	6	289,136	648	2 2
N E Metropolitan	3,063,200			4	225,032	260	1 2
S E Metropolitan	3,197,400	2423	76	6	304,447	740	2 4
S W Metropolitan	4,672,410	3055	65	10	386,186	691	1 8
Oxford	1,484,810			3	146,242	182	1 2
South Western	2,752,000	1729	63	6	266,375	350	1 3
Welsh	2,603,000	2103	81	6	221,563	342	1 5
Birmingham	4,547,000	3587	79	6½	351,314	1220	3 5
Manchester	4,400,000	2559	58	6	274,116	380	1 4
Liverpool	2,095,000	2058	98	4	181,329	623	3 4

Infectious Cases

In recent years just under half of the active cases had tubercle bacilli demonstrated in the sputum (or in stomach washings or pleural fluid)

In 1954 41% (556) of the patients with active tuberculosis were excreting tubercle bacilli In 1955 the proportion rose to 48% (591) and in 1956 to 49% (602) These findings came from the reports of the physicians who took over the care of the cases There is little doubt that the percentage may be even higher, for the search for tubercle bacilli is not made with the same intensity in all clinics and hospitals It must be emphasised that these percentages relate to all groups and surveys, and the percentage is much higher among active cases found in patients sent by doctors Here the figure reached 67 7% (429) Brett et al (1956) in the Islington survey found that 59% of the active cases in male Islington residents referred by doctors were infectious The corresponding figure among active cases in females was 54%

Contribution to Case-finding

The only way I have been able to assess how far mass radiography has contributed to case-finding in the region was by estimating the proportion of mass-radiography cases notified to the total notified cases in the region Cases discovered by mass radiography were notified by the clinic or the hospital physician, who, it must be assumed, used the same criteria for notifying a case referred by mass radiography as he would for a case referred from any other source

I have been able to obtain details only for 1955 and 1956 Of 4107 newly notified cases of respiratory tuberculosis in 1955, 1098 (26 7%) came from mass radiography In 1956 the proportion was slightly higher 1115 mass-radiography cases were notified out of 3587 cases (30%) The proportion was, of course, much higher in areas where sessions for doctors' patients were held For example, in Wolverhampton, Birmingham, and Stoke 52%, 45%, and 43% respectively of all new notifications of respiratory tuberculosis in 1956 were of cases discovered by mass radiography

Lastly, it is useful to know how the work done in this region compares with the results obtained elsewhere in England and Wales Table IV shows these results and has been compiled through the courtesy of the senior administrative medical officers of regional hospital boards in England and Wales In studying this table allowances must be made for the lower tuberculosis incidence in some areas, for different methods of using mass radiography, and for the emphasis placed on the service by the regional hospital board and the tuberculosis service In the Birmingham region both the board and the tuberculosis advisory committee have consistently supported and encouraged the development of the service The table shows clearly that their confidence in mass radiography as an effective method of case-finding has not been misplaced

Discussion

Nash (1956), who has given much valuable advice on the use of mass radiography in case-finding, has pointed out that ingenuity and imagination must be used, and the situation in the area served must be constantly reappraised

In the Birmingham region the use of mass radiography has been based on the assumption that its most valuable contribution would be to find quickly as many cases as possible of active tuberculosis Consequently the whole scheme for the deployment of the units and their method of working was drawn up with this aim in view The temptation to organise surveys with a view to finding lung cancer, heart-disease, or pneumoconiosis had to be resisted

Mass-radiography case-finding activities fell into two main categories First, and most rewarding, were group-radiography sessions for high-prevalence groups, such as patients sent by general practitioners, contacts, self-referred persons, and tuberculin-positive children Secondly, there were mass surveys of factory employees and the general public, where the purpose was to X-ray large numbers of persons as expeditiously as possible so as to filter off the cases of symptomless active tuberculosis These mass surveys needed to be undertaken with imagination and, with careful planning, yielded a satisfactory return of active cases

In addition to case-finding, protective surveys were also held, the intention being to protect either the group or the individual rather than to find a high incidence of tuberculosis These surveys included groups such as National Service recruits, antenatal patients, students, and persons working with children

The idea of using units in a mobile role with a return to a base centre at regular intervals worked well in practice The apparatus and vehicles, being heavy and cumbersome, were difficult to manœuvre in the congested roads of the Midlands, and all the units felt the need for a lightweight mobile unit which could be operated from an ordinary power point One unit tried the experiment of visiting four centres at regular intervals for group radiography, mainly of general practitioners' referrals The results in the selected areas were most encouraging, and, until more static units are provided, this type of service is well worth developing

The combination of group and mass radiography used by units in 1956 produced 1220 active cases This is the highest number of cases discovered in any region although the actual prevalence is not so high as in the North-East of England

It is worth noting that about half the active cases were infectious The early minimal lesion of routine mass radiography is replaced in group radiography by a more extensive, sometimes cavitating, condition It must be conceded that such lesions should have been detected clinically That they were not so detected makes the value of the service more significant, for a source of infection in the community has been found and removed Thus the search for contacts, although important, has not the same urgency as when a minimal lesion is discovered and the infector remains at large in the community

These results enable us to see, although dimly, the pattern for the most effective use of mass radiography in the future. Units should consist of two parts—a static 100 mm unit for group radiography, and a lightweight mobile component for mass surveys of selected high-prevalence groups The static unit should be placed in the main hospital for the industrial area, where the mass radiography organisation could use it according to the local demand twice daily sessions would be needed in a city the size of Birmingham, in smaller cities sessions two or three times a week would suffice At other times the unit would be available for routine X-ray of outpatients and for follow-up cases The mass-radiography service could undertake this work now, for it already has the filing and record system as well as the trained personnel to handle the numbers likely to be referred for X-ray The medical director is trained and experienced in reading miniature films, and through his present work has close contacts with the local general practitioners, who would be the main users of the service The mobile unit, which would be used on a diminishing scale as time goes on, would concentrate mainly on groups or districts where there is a high incidence of tuberculosis

The policy of using mass radiography in both static and mobile roles widens considerably the line of attack on tuberculosis It also enables a balanced service to be achieved. "Balance," according to Lord Montgomery of Alamein, "implies the disposal of available forces in such a way that it is never necessary to react to the enemy's thrusts and moves, a balanced army proceeds relentlessly with its plans in spite of what the enemy may do" Tuberculosis is the enemy Mass radiography must attack with a balanced army of two corps the static corps for group radiography and the mobile corps for mass radiography It is only when thus deployed that it can "proceed relentlessly with its plans" and make victory inevitable

Summary

The use of mass radiography in the Birmingham region in 1952–56 is described.

During these five years more than 1000 cases of active tuberculosis have been discovered annually, giving a prevalence-rate, in recent years, of 3–4 per 1000

The increasing value of group radiography of high prevalence groups is emphasised

In 1956, 30% of all the notified cases of respiratory tuberculosis in the region came from the mass-radiography service.

A mass-radiography service combining a static unit for group radiography and a lightweight mobile unit for mass surveys is advocated

For information about mass radiography in their regions my thanks are due to Dr P J H. Clarke, Dr J O F Davies, Dr J Fairley, Dr J Graham, Dr G H. Hall, Dr T F Jarman, Dr G C. Kelly, Dr J S B Mackay, Dr D L. Murray, Dr J A. Rushworth, Dr G C. Taylor, Dr A. B Williamson, and Dr F L. Wollaston.

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— Benjamin, B, Lee, T J (1953) *Brit med J* i, 304
Sutherland H. (1952) *Lancet*, i, 152.

Scotland in 1957

In his preliminary report of the Scottish vital statistics for 1957, the Registrar-General estimates the population as 5,159,500 at the end of the year The marriage-rate, though still high at 8 3 per 1000, had fallen a little from the 1956 level, but the birth-rate rose to 19 per 1000, and as the death-rate stayed about the same there was a natural increase in the population—of 36,835 But the net migration from Scotland was 35,500—20,000 to Canada and most of the rest to England.

The maternal mortality rate (1 in 2000) and infant-mortality rate (29 per 1000) were the same as in 1956 The expectation of life, based on the 1957 figures, is 65 8 years for boys at birth and 71 3 years for girls These figures are respectively 21 and 24 years more than those at the beginning of the century

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Special Articles

CONTRACEPTIVE TECHNIQUE

ON March 4 Dr Sylvia Dawkins gave a lecture-film demonstration on contraceptive technique for final-year students of all London medical schools

Prof W C W **NIXON**, the chairman, said that every medical student before qualification should be educated in this vital question, and that ideally such instruction should be given in a contraceptive clinic attached to each teaching hospital's postnatal department. Unfortunately this was not done today, and it was left to the Family Planning Association to sponsor such lectures as this in an attempt to fill the gap in present-day medical training Professor Nixon spoke of the 268 F.P.A. clinics throughout the country and of the work of the Association, which had reached its present position only after twenty-seven years of struggle against the prejudice and misunderstanding which had for so long obscured this subject.

Dr **DAWKINS** described the medical indications for advice on contraception, and spoke of the social aspects of this question, stressed in the report of the Royal Commission on Population nearly ten years ago but still sadly neglected It was not enough to recommend patients to limit, or space their families, the doctor must be able to give practical advice on how to carry this out. Some municipal clinics gave advice on contraception, and this service was provided over a wide area by F.P.A clinics The various methods were discussed, and the techniques of fitting and using occlusive caps were described and illustrated by a film In conclusion Dr Dawkins said that this was a world problem necessitating continuous research for simpler and more acceptable methods of family limitation than those now available.

In England Now

A Running Commentary by Peripatetic Correspondents

THIS was it I had chosen my surgeon, bought him the latest book on operative technique, and promised him frozen sections after my recovery About to lose my piles, it was now imperative that the Consultant Pathologist to 1250 beds did not lose face So, having sent a strong letter to the Physician-Superintendent protesting that the various weaknesses of his administration were having a deplorable effect on the pathological service, I confidently entered the ward The Physician-Superintendent followed unexpectedly, the letter in his hand, thanked me for it, apologised for its necessity, promised that the deficiencies would be attended to immediately, wished me a speedy recovery, and departed master of the occasion A second demoralising deflation soon followed, this time by the Ward Sister What was my name please, she knew she ought to know, but she didn't and there it was, from the laboratory wasn't it? With the score 2-0 to the opposition I seized on the bedside lamp in a desperate bid for recovery It had no shade, the switch cover was broken, and various live parts were dangerously exposed Could Sister please have it sent to the Engineer with the Pathologist's compliments, and ask him if it was not below his usual standards for hospital equipment? Feeling better, I approached the probationer nurse with gracious apologies for the postponement of her bacteriology lecture and demonstration, as a result of my forthcoming operation Oh, was there a postponement? She had had her lecture two years ago, when the cultures had not grown, the slides had got mixed up, and the curtains caught fire My lectures were only for prelim candidates, she was taking finals shortly

I know when I am beaten The prolapsed parts were removed without further trouble, they were not sent for section, and convalescence proceeded without a bedside lamp

* * *

As I strolled through the Embankment Gardens I could have sworn that I saw a ring-ouzel at the far end It was a dark bird bearing, where his neck met his breast, something white, wide, and crescentic like a Celtic chieftain's torque (the ring-ouzel's specific name is *torquatus*) The locality and the season, however, were wrong, and a second look showed me a "feral" pigeon which had obviously been pecking, in a complete round of stale bread, a hole which was big enough to take his head and had done so, with the result that, supported only by a thin rim of crust on the back of the pigeon's neck, a bib of sliced bread dangled, just where the bird could not peck it, like Aaron's breastplate Strangely enough none of his congeners sought the hospitality of his real sandwich-board, nor did the latter much impede his movements I tried to catch him, but he flew with the greatest of ease, carrying his urim and thummim [1] before him, on to the National Liberal Club Is this a political omen?

* * *

The speaker was a distinguished elderly lady To the best of my knowledge I had never seen her before and her face was quite unfamiliar to me However, when my eyes wandered, I became aware that I knew her legs Every inch and every curve below the skirt was completely familiar to me As I sat pondering this matter, in the back of my mind were vistas of a lawn in summer and of a huge monkey tree, the sound of croquet balls echoed in my imagination

I made a deduction from this experience and later questioned my mother about it She informed me that the lady had been a neighbour of ours when we lived in —shire in a house we left before I was three years old She used to come and play croquet with my parents on the lawn, beside the monkey tree

My deduction appears to have been correct What we remember and recognise in each other is not specifically the face, but whatever is at eye-level

* * *

After twenty-five years the towpath at Cambridge is dangerous place for the meanderings of a peripatetic cor spondent First there's the bicycle, with only half a pedal one side and handlebars so low as to permit a view of t ground alone, coaching the boat becomes secondary to keepi out of personal danger Other cycles approach following bo coming upstream More alarming still is the slot between t railings Is it wide enough for the handlebars to go through And if so, is one steady enough to avoid fouling one side? N time to get off, besides pride will not permit With a sigh relief the other side is reached without taking a tos Emboldened by this one looks at the boat only to forget th the railings at the edge by the gasworks take a sudden ste inwards to the discomfiture of those who are not looking ahea But by the time Baitsbite is reached I have become accustome to the constant possibility of sudden projection or sidewa slither into icy water, caution is abandoned, and attentio turned solely to the crew a good ten-stroke practice star then the full course row They are going quite well, a lot water coming by "Well rowed, boys" The words actuall pass my lips Slightly ridiculous, of course, from a grey-haire staid, and surgical self It doesn't matter, nobody's lookin They are round First Post Corner now "Give her ten, boy into the straight"—a real shout But, alas, where does th derisive laughter come from? How did my three daughte get there?

* * *

From the seclusion of a single-bed ward hospital noises a an interesting study The rattle of cups and plates in the war kitchen are easily accounted for, and the reverberating con versation of the night staff is self-explanatory The rattle an crash of the lift gates is generally easy to integrate with th working of the lift, although it is not clear why they have t be violently and noisily kicked at irregular intervals Perhap it is the call sign of the hospital grapevine, and the subsequen gibberish shouted up the lift shaft is the football scores Bu the real puzzle is the periodic noise of a trolley load o crockery being wheeled on to the lift from the top floor whe the said lift is at the bottom The catastrophe makes n impression on hospital routine, the lift continues relentlessly to shuttle unimpeded by debris or damage, and crockery never runs out Can it be that hospital flying saucers are real-life ones in negative phase?

* * *

EPONYMS

One of my more eccentric whims
Is that I don't like eponyms
Once I did like them—now I see
Their limited utility

A name should make a fact shine bright
But eponyms oft hide the light,
They give no date and no location
And never offer explanation

I almost hear the student's groans
When he is faced with two unknowns
And see his trembling lips recite
"What's the disease?" and "Who is Bright?"

Of course an eponym may be
Some use in medicine-history,
But of those used I think a lot
Had better far be quite forgot,
And many names we all must own
Would otherwise be quite unknown
For all the greatest "hers" and "hims"
Have no great need for eponyms

Three eponyms—two signs, one test—
Now bear my name, without request,
I surely would be much to blame
If I should here subscribe my name

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[1] See *Exodus*, 28, 30

Letters to the Editor

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—The main reason for the repair of inguinal herniæ remaining a problem is the wide discrepancy between the monotonous excellence achieved in personal series and the uniformly depressing results obtained by impersonal statistical reviews Almost complete success has been achieved, by using the Bassini operation and by *not* using the Bassini operation, by using catgut, linen thread, floss silk, fascia lata, strips of external oblique fascia, silver filigrees, tantalum gauze or wire, dermal grafts, and now nylon. Yet impersonal reviews indicate that the recurrence-rate remains excessively high and fairly constant, whatever method or material is employed

The quota of human ingenuity in designing repairs for hernia was filled soon after the turn of the century, so that it is only natural that we should endeavour to discover the ideal suture material. It is here, rather than in the type of operation, that we have failed by not following our ideas through to a logical conclusion. Take the silver filigree, for example, which has provided excellent results in the past. During the war, when filigrees were virtually unobtainable, I suggested a cheaper and equally effective substitute—namely, the tops of tobacco tins Apart from providing an indestructible barrier, they possessed the added merit of assuring an immunity to boils while the tin-plating lasted and then serving as a reservoir of iron which would keep the patient in perfect health to the brink of the grave and even beyond. The dermal graft taken from the pubic region again pointed the way Surely this was only a precursor to the inlay carpet graft and should have opened a wide field for the study of the respective merits of Aubusson, Wilton, Axminster, &c. Now what happens if nylon should fail too? Do we retire to 'Rayon', which makes safe motor tyres, or advance boldly to 'Terylene', which provides indestructible socks?

The only solution, as I see it, is the widest encouragement to the publication of personal series, as authorship and good surgery appear to be synonymous, and the ruthless suppression of all impersonal statistical reviews

Law Hospital, Carluke,
Lanarkshire.

W J M BRANDON

SIR,—As an argument has started already about the chance of sinus formation following the use of monofilament or multifilament nylon I wonder if I might make a few remarks

Rightly, it has been said in criticism that, unlike scientists who discuss a problem, we dispute like theologians This criticism is justified, and it is interesting to witness the development of the present dispute. Mr Haxton (Feb 22) states that a chronic sinus with monofilament nylon is almost unknown, Mr Seth-Smith says "rot," in both meanings of the word. Mr McMaster, if I understand his letter of March 8, agrees with Mr Haxton because he says he has not needed to remove any monofilamentous nylon in the past 5 years Mr Marsden (March 8), however, sides with Mr. Seth-Smith and repeats, "rot."

This vigorous disagreement is of the same sort that has bedevilled the quest for surgical knowledge for fifty years in problems of this kind. Writers assert that if only their deluded colleagues would abandon their defective techniques and follow their lead the problem would be solved. These deluded colleagues, however, reply with a brusque contradiction, accuse them of talking nonsense, and imply that they may be guilty of prevarication. The present dispute is confined to two types of nylon suture, but it is part of the wider dispute, of which type of technique to use when repairing a hernia, which has wrangled on, without conclusion, through tens of thousands of published case-reports, for many years

The notion that, provided a sufficiently large number of disputes, covering a sufficiently large number of cases, can be perpetuated for a sufficiently great length of time, the 'solution" will crystallise out automatically is false. If this notion were not false, if it were not a spurious guide, the solution to this, and allied problems, would have been reached years ago

Problems like the present one are not peculiar to surgery, they occur in the biological sciences and Professor Fisher[1] has described one way at least of tackling them Recently I described[2] a pilot test on five rival types of herniorrhaphy conducted on the lines Fisher has indicated, and it seems to me that, unless such tests became routine surgical practice, bootless arguments, like the present one, will go on for ever

Bromsgrove, Worcs.

F S A. DORAN

SIR,—Surgeons who argue about the different tensile strengths of unabsorbable suture materials go wrong in imagining that it is the actual sutures which prevent the hernia from recurring How can this be so when many herniæ are cured by repair with catgut, and some with no sutures at all?

The defect left after removal of the sac is best closed by the patient's own muscular mechanism Once the surgeon has decided that the hernia is too large for this to happen, he must see to it that the gap is closed by strong scar tissue which will not stretch under tension applied to it throughout the years No unabsorable suture, fabric net, or metal mesh will do this if the tissues which hold it yield under tension These materials are only effective to the extent that they stimulate fibroblastic processes which lead to the laying down of an unyielding scar The most effective agents in this process are grafts of dermis or fascia lata, but these have proved to have inherent disadvantages Floss silk is just as good and rarely gives rise to sinuses if buried beneath the aponeurosis of the external oblique (although it sometimes gives trouble when used for the linea alba after laparotomy)

Let us not flatter ourselves that it is our stitching alone, however skilled, which cures the hernia If the patient's own fibroblasts do not play their part failure is certain.

Whiston Hospital,
Prescot,
Lancashire.

J. A. MARTINEZ.

DEFICIENCY DISEASES IN BRITAIN NOW

SIR,—I was interested in the recent accounts of deficiency diseases (Feb 15, p 354, March 1, pp 454, 477) In the present vitamin-conscious times and age of plenty frank vitamin-deficiency states are often said to be uncommon. Several years ago we were authoritatively told[3] "that in Great Britain fully developed states of vitamin deficiency such as beriberi, scurvy, and pellagra are very rarely encountered" Only a few miles away, however, in the Stobhill General Hospital, Glasgow, not less than 100 patients were admitted with florid scurvy in the fifteen years before 1954[4] It seems, therefore, that the distribution of these comparatively rare deficiency states is far from uniform

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[1] Fisher R A. The Design of Experiments Edinburgh, 1947
[2] Doran, F S A. *Ann. Surg* 1957, 146, 957
[3] Davidson, L. S P *Brit med J* 1949 ii, 1036.
[4] Thomson, T J *Glasg med. J* 1954, 35, 363.

When Prof V P W Sydenstricker was sent over from the United States to study deficiency diseases in war-stricken Britain, he "complained" to me that he saw only 2 such cases in a month's travelling up and down the country During a single afternoon I could show him 12 cases of pellagra in two London hospitals [5]

The presenting symptom of many of these conditions is often deceiving, e g, one of the above pellagra cases was sent back from Midhurst to a general hospital because she became "unmanageable", another landed for similar reasons in another general hospital, in Dr Baron and Mr Oliver's patient the suspected diagnosis was subdural hæmatoma or cerebellar tumour Of my patients with Wernicke's encephalopathy, a brain tumour was first diagnosed in one and uræmia in another [6]

In May, 1957, I saw a middle-aged lady doctor on account of sudden obesity Within a few weeks she became so bulky around the girdle that walking became difficult Her tiredness, weakness, and breathlessness were mainly attributed to the quick gain in weight Since the bombing of London she had drunk heavily On examination she was confused though not disoriented A proper history of recent events was impossible She had ataxic gait, rombergism, horizontal and vertical nystagmus, and diplopia All tendon reflexes and vibration sense below the knee were absent, she had hyperæsthesia of the Achilles tendon There was severe muscular wasting, mainly of the lower arms and particularly of the hands Her grip was very weak She had a fiery red tongue with stomatitis The heart was enlarged, the QT interval in the electrocardiogram (E C G) was significantly prolonged, and U waves were present The serum-potassium was normal She had gross ascites Her blood-pyruvate content was high

Treatment consisted of a protein-rich nutritious diet, and parenteral administration of the whole vitamin-B complex Diplopia disappeared, the E C G became normal on the fifth day in hospital, and in three weeks she lost 10 kg of weight in spite of good appetite Ascites disappeared After discharge she continued to have injections of aneurine (25 mg every second day) and vitamin-B complex by mouth By October she was back at full work, after this fulminating attack of beriberi

As the storage facilities for water-soluble vitamins are limited, treatment should be conducted for many months with comparatively small doses of B vitamins, and not by flooding the patients with very large doses for a short time

It appears, therefore, that major deficiency states in this country are commoner in everyday practice than one would expect from textbook accounts A further possible reason for this discrepancy may be that some of the vitamin-deficiency states are part of the malabsorption syndrome, and are often registered under this heading Thus I encountered recently a patient in a London hospital who had intractable multiple avitaminosis which was part of the protein malnutrition (kwashiorkor) syndrome [7]

Finally, I should like to underline Dr Cutforth's statement (March 1) that the clinical picture of scurvy in his cases differed from the descriptions found in current textbooks, and he particularly mentioned the absence of bleeding gums Not long ago we emphasised [8] that boggy, bleeding gums are exceptional in elderly, edentulous patients, with shrunken and atrophied gums, suffering from scurvy As scurvy in this and othe Western countries is chiefly encountered nowadays i elderly people living alone or in institutions, perhaps i would be timely to correct the present teaching, which is a relic from times when food was scarce for large section of the community, and the incidence of scurvy wa greater in the younger age-groups

London, W 1 Z A LEITNER.

CORTISONE IN THE TREATMENT OF ACUTE INFECTIONS

SIR,—In his letter of March 15, Mr Louttit suggest that intramuscular hydrocortisone may have hastened th death of a patient with pneumonia When hydrocortison or like-acting corticosteroids are given in excess of th body's needs the endogenous supply of hydrocortisone is quickly cut off My limited experience of febrile patient and patients with pneumonia suggests that their adrenal may produce 40–80 mg or more of hydrocortisone a da The slowly absorbed intramuscular hydrocortisone give to Mr Louttit's patient is not likely to have raised hi tissue hydrocortisone levels at all before he died

The problem of when and how to use cortisone-lik steroids in severe infections would be advanced if mor studies were made of the adrenal's output of hydrocortisone during such infections The necessary studies ar long overdue If the studies provided evidence of optima levels of hydrocortisone production in various circumstances, then such levels could be assured by administering the appropriate amount of the most suitable corticosteroi —without any qualms

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Sheffield H F WEST

TECHNIQUE OF INTRA-ARTICULAR INJECTION

SIR,—The lateral patellar approach to the knee-joint has several advantages over the "*patellar tendon*" approaches mentioned by Mr Grant Waugh [1] Although the latter routes are often convenient, there are sometimes unexpected difficulties due to osteophytes and hypertrophied ridges over the anterior marginal aspects of the tibial condyles, cartilaginous and bony destruction may narrow or obliterate the intrasynovial cavity at these situations, and there is the danger that the needle point may further damage diseased cartilage at a weight-bearing area

The technique described by Mr Kaplan (Feb 15) is sufficient in many instances, but Mr Harrison (March 1) has made the valid point that distended joints with tense capsules are more easily entered To achieve this condition when the knee-joint is not already swollen with an effusion the following procedure has been found useful

With the joint flexed and supported at an angle of about 25°, a figure-of-eight domette or elastic bandage is wound firmly around the knee in such a manner as to leave a diamond-shaped area of skin exposed over the lateral aspect of the patella Excess synovial fluid in the suprapatellar and posterior synovial recesses is squeezed anteriorly and a taut, bulging capsule is presented at the exposed area The capsule may be pierced and the intrasynovial cavity entered about $^1/_2$ in below the superior border and just below the lateral margin of the patella

In addition to simple and comparatively painless joint puncture, this method allows easy aspiration of fluid for diagnostic purposes, and the joint may be more completely emptied of synovial fluid before injection of hydrocortisone or prednisolone suspension. This last point is important inasmuch as excess synovial fluid dilutes and hydrolyses hydrocortisone,[2] and in clinical practice preliminary aspiration of an effusion has been shown to permit a better therapeutic response to intra-articular steroids [3]

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[5] Rimington C, Leitner Z A *Lancet*, 1945, ii 494
[6] Leitner Z A *ibid* 1952, ii 1229
[7] Leitner Z A *Proc Nutr Soc* 1958, 17, rc
[8] Leitner, Z A, Church, I C *Lancet*, 1956, i, 565

[1] Waugh, W G *Lancet*, 1957 ii, 1311

I feel that the points raised by Mr Harrison in the final paragraphs of his letter require some modification Although the primary indication for intra-articular steroid therapy is an active, inflammatory, non-infected arthritis (chiefly rheumatoid arthritis) such a condition is by no means invariably associated with an effusion or distended joint capsule Conversely, many distended joints indicate a chronic effusion with little or no residual inflammatory process, and although joint puncture in these instances is simple the benefit derived from intra-articular steroids in such patients is trivial or nil

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MALCOLM THOMPSON

CLINICAL GERIATRICS

SIR,—Dr Trevor Howell (March 8) asks " Is it not time to press for more clinical instruction in geriatrics ? " May I ask what constitutes clinical instruction in geriatrics as compared with any other clinical instruction ? That geriatrics has its own administrative problems I can understand, but do the clinical signs of any disease differ in any way in a patient of, say, 68 from those in one of 50 ?

London, W 1

M H PAPPWORTH

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—Dr Pasmore (March 8, p 535) bases his letter upon a surmise. Had he read my letter again, instead of dashing to *The Medical Directory*, he would have realised that it contained no denial of the importance of functional disorders or of psychotherapy I am, in fact, prepared to compete with most G P.s in hours spent per week in this field. My objection to the approach of those with Dr Clyne's orientation is not that they criticise the widespread neglect of the psyche but that they contribute to the still-general scepticism about psychiatry by insisting upon a subjective approach which withdraws psychiatry from the arena of science

This tendency is exemplified in Dr Pasmore's letter when he states that if a " scientific inquiry related to the function of the stomach " shows no abnormality we must diagnose a functional disorder and give simple reassurance. This is funny science, the function of the stomach is known on anatomical, physiological, and clinical grounds to be influenced by mental and emotional changes and a truly scientific approach will recognise this According to Dr Pasmore, however, we can only go beyond reassurance " when we can make a personality change " This is of course, not true Bad teaching in medical school and, for some, personal difficulties may prove obstacles to understanding neurosis, but Dr Pasmore must please accept that many of us, none the less, do achieve a reasonable understanding without undergoing personality change Psychotherapy is not just the oozing of the suitably modified personality of the therapist, it is an activity and a relationship based, if still all too insecurely, upon a knowledge of human behaviour and the use of certain communicable techniques That detached, scientific investigations of the causes of neurosis, the nature of psychotherapy and the effects of psychotherapy are difficult, none will deny, that so few are attempted (and that subjective, non-communicable, and non-testable methods are so widely preferred) is surely a matter of regret.

London, N W.5

ANTHONY RYLE

ESSENTIAL FATTY ACIDS AND IDIOPATHIC HYPERCALCÆMIA OF INFANCY

SIR,—Dr James and his colleagues, in your issue of March 8, conclude that their " results do not provide any evidence that an essential fatty-acid deficiency is a cause of, or is present in, infants with idiopathic hypercalcæmia " To the general reader it may not be apparent that their interesting results do not necessarily provide any evidence against these possibilities

In your columns [1 2] and elsewhere [3] I have suggested that this disease is caused by a diet low in essential fatty acids (E.F.A) and high in calcium and vitamin D, for the following main reasons

(1) Almost all the infants who have developed the disease have been fed on dried cow's milk and not on human milk or evaporated cow's milk.

(2) Fresh cow's milk is known from the work of Hansen to be deficient in E.F A as compared with human milk.

(3) Dried cow's milk in the presence of oxygen (and presumably unhydrated metallic ions which act as catalysts) loses E.F A on storage

(4) Cow's milk is richer in calcium than is human milk, and a minimum amount of vitamin D in dried cow's milk is required by law

(5) Infections increase the requirement of E.F.A and this might explain the association of the disease with interstitial plasma-cell pneumonia in Finland

(6) I have found that rats deficient in E.F A have a greatly increased sensitivity to vitamin D as compared with control pair-fed rats ingesting an equal amount of fat, and quickly die from uræmia caused by nephrocalcinosis

(7) It is generally agreed [4] that in idiopathic hypercalcæmia of infancy there is increased sensitivity to vitamin D This increased sensitivity could explain the signs except for three of them and these could also be explained by deficiency of E.F.A. the mental changes (since the normal nervous system is rich in E.F.A.), the raised serum-cholesterol, and the atheroma (alleged by Bonham Carter et al [5] to be the cause of the hypertension and systolic murmur) If the cause of idiopathic hypercalcæmia of infancy is a diet low in E F.A. and high in calcium and vitamin D, administration of a rich source of E F A such as cotton-seed oil should lower serum-calcium, and this has now been demonstrated by James et al.

The two lines of possible evidence against my view may be summarised and refuted as follows " Sinclair's claim is not supported by analyses of different preparations of cow's milk for their essentially [sic] fatty acid contents " Here Stapleton and his colleagues [4] are quoting James, and in the paper in your issue of March 8 the evidence is given

Two samples of human milk contain 5 1% and 4 4% of fatty acids as linoleic—linolenic acids, corresponding figures for cow's milk immediately after roller drying and after storing for 3 and 6 months at room temperature (whether in air or not is not stated) are 3 4%, 2 3%, and 1 4% Though the figure for fresh cow's milk agrees with those given by Hilditch in his recent summary,[6] the two figures for human milk are lower than those cited by Hilditch, the mean of which is about 8%

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[2] Zacco, M Richardson, E. M Crittenden, O , Hollander J H Dohan, F C. *J clin Endocrin* 1954 14 711

[3] Stevenson, C. R., Zuckner J Freyberg R H *Ann rheum Dis* 1952, 11, 112.

[1] Sinclair, H M *Lancet*, 1956, ii, 101

[2] Sinclair, H M *ibid* p 893

[3] Sinclair H M Proceedings of 3rd International Conference on Biochemical Problems of Lipids, 1956 p 302

[4] Stapleton T MacDonald, W B., Lightwood, R. *Amer J clin Nutr* 1957 5 533

[5] Bonham Carter R. E Dent, C.E., Fowler, D I , Harper, C M *Arch Dis Childh* 1955, 153, 399

But even taking the figures of James et al, dried cow's milk which has been stored is likely to be lower in linoleic acid than fresh human milk, of course storage can occur in various ways and only a very small proportion of infants fed on dried cow's milk develop idiopathic hypercalcæmia But this is not the whole story James et al state that "Linolenic acid can exist in three forms—cis-cis, cis-trans, and trans-trans—but only the cis-cis form can be utilised" Every part of this statement is wrong There are eight possible geometric isomers of linolenic and four of linoleic acid, which is probably meant So far as is known all four isomers of linoleic acid can be utilised in the body for energy, but only the cis-cis form can act as E F A Hilditch[6] cites many authors in support of the view that almost all the linoleic acid in human milk is this cis-cis isomer, whereas in cow's milk only "minute proportions" consist of this isomer and most of the linoleic acid is a trans isomer which does not have E F A activity This, as shown by Shorland and Reiser and others, is because of bacterial action in the rumen of cows the pasture-fed cow eats about 60% of its fatty acids as all-cis-linolenic acid, and yet only traces of this acid in any form appear in the body-fat or milk because bacteria hydrogenate it and during this process isomerisation occurs James et al counter this mass of evidence by stating that "Van Beers et al (1957) have shown that about 50% of the linoleic acids of cow's milk is in the cis-cis form, so it cannot be claimed that infants fed on cow's milk are being provided solely with the wrong isomer"

Van Beers et al reported, I believe, only one value for the cis-cis-linoleic acid in winter butterfat—namely, 1 9%, and stated that the amount in samples of summer and winter butterfat is between 1% and 2% If this is compared with the usual content of cis-cis-linoleic acid in human milk of about 7% or 8% it is not surprising that Hansen and his colleagues have demonstrated in infants a deficiency in fresh cow's milk as compared with fresh human milk, which deficiency is completely abolished by isocaloric substitution of the fat of cow's milk with vegetable seed oil as a rich source of cis-cis-linoleic acid James et al dismiss on chemical grounds the possibility of diminution by trans-isomerisation during drying of the already low content of cis-cis-linoleic acid in cow's milk but other chemists have told me such a change is likely, in some preliminary experiments on rats I found that National dried milk had less E F A activity than fresh cow's milk, though I did not test the same samples before and after drying, since James et al show that there is no loss in total linoleic acid on drying, my results could be explained by trans-isomerisation

Clearly more research should be done upon this Whatever the result, it cannot be disputed that fresh cow's milk is much lower in E F A than is human milk, as judged by chemical analysis and confirmed by Hansen's tests on infants, and there can be a fall in content of E F A upon storage of dried cow's milk in air so that some infants fed on dried cow's milk can be consuming even less E F A than infants fed on fresh or evaporated cow's milk and considerably less than breast-fed infants

I have compared at length cow's milk and human milk as sources of E F A because this is a matter of great importance As an illustration I might mention that at a conference in California which Dr James and I have just attended Dr Stanley Hartroft extended his very interesting results on the dietary production of myocardial infarction in rats by showing that rats given cholesterol, sodium cholate and thiouracil (which increase the requirement of E F A) develop myocardial infarction if fed cod-liver oil with a hydrogenated fat or if fed butter (both of which sources of fat are low in E F A) but not if fed corn-oil with a hydrogenated fat (corn-oil is high in E F A)

The other line of possible evidence is that the amounts of E F A in the blood of three infants with the disease were similar to those in three normal infants

It is well known that in lower animals when linoleic acid in blood falls after dietary deficiency of E F A the content of trienoic acid rises, and Hansen and his colleagues have confirmed this in infants[7] Therefore the combined estimation of linoleic+linolenic acid might remain normal and conceal a deficiency, as pointed out by James et al who discount this possibility because the amounts of arachidonic acid fall within the normal range But Hansen has found lowered dienoic, raised trienoic, and normal tetraenoic acids in infants with skin signs attributed to deficiency of E F A and cured by this therapy Deficiency of a nutrient can occur in tissues when the concentration in blood is normal pellagrins have normal amounts of nicotinic acid in blood Further, infants fed on dried cow's milk are certainly ingesting greater amounts of trans polyenoic acids than infants fed naturally, and these amounts would be estimated by gas-chromatography along with E F A but would have no E F A activity So this evidence, though interesting, is by no means conclusive

I continue to believe that idiopathic hypercalcæmia of infancy is probably caused by a diet low in essential fatty acids and high in calcium and vitamin D

Oxford H M SINCLAIR

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[6] Hilditch T P The Chemical Constitution of Natural Fats London 1956

[7] Hansen A E, Adam, D J D, Boelsche, A N, Haggard, M E, Wiese, H F Proceedings of 4th International Conference on Biochemical Problems of Lipids, 1958 (in the press)

CARDIAC ARREST FOLLOWING ELECTROPLEXY

SIR,—The letter from Dr Crowley (Feb 15) is of considerable interest to me At our hospital there was a similar event a year ago I therefore undertook a detailed study of the immediate cardiac effects of electroconvulsive therapy The great problem in such an investigation is to determine exactly what happens to the heart during and just after the shock The studies of Bellet and Aultschule several years ago reported only cardiac arrhythmias I now have clear evidence that a brief period of asystole may occur This can be prevented only by a relatively large dose of atropine (1-2 mg) or other anticholinergic drugs given about 30 minutes before the shock The arrest of the heart is not necessarily related to the thiopentone and suxethonium bromide, but rather to the status of the heart, the voltage applied, and the duration of the shock

Department of Anæsthesia,
University of Saskatchewan College of Medicine
ALLEN B DOBKIN

RIBONUCLEASE ACTIVITY IN CHRONIC GRANULOCYTIC LEUKÆMIA

SIR,—A group of biochemists in this clinic, Ostrowska, Urbańczyk, and Spirer, have measured the activity of ribonuclease (RN-ase) in serum and urine by the modified method of McCarthy

This method consists in adding ribonucleic acid to the fluid being examined and estimating, after precipitation by *N* hydrochloric acid, the turbidity caused by the excess acid not decomposed by the RN-ase in the fluid The turbidity is measured by Pulfrich s photometer, and the RN-ase activity is found by comparison with a curve drawn from results with pure crystalline RN-ase

In 16 healthy people the serum content varied from 0 53 to 0 92 mg per ml (when 1/1000 dilution of serum was used), the activity in urine ranged from 2 77 to 22 0 mg per 24 hr But in 33 cases of chronic granulocytic leukæmia, the activity was as high as 300 mg per 24 hr, though the serum content was no higher than normal There was some correlation between the RN-ase content on the one hand and the severity of the disease and the height of the granulocyte-count on the other In 9 cases of chronic lymphatic leukæmia, in cases of reticulosis (including 10 of myeloblastosis and 3 of lymphogranulomatosis), and in 15 cases of infectious disease with leucocytosis, the RN-ase activity was normal in both serum and urine

The increase in the RN-ase activity in the urine in chronic granulocytic leukæmia is so specific that in doubtful cases it helps to make the diagnosis [1] [2] What bearing, if any, this phenomenon has on the causation of leukæmia remains to be seen

IIIrd Clinic for Internal Diseases,
Academy of Medicine,
Krakow, Poland
JULIAN ALEKSANDROWICZ

NO PEACE FOR THE PATIENT

SIR,—When I was a hospital almoner, one of my tasks was to persuade people to come into hospital "Apart from all the other advantages, you will have a good rest," I used to say But I have been an inpatient myself recently, and now know better

I was on complete bed rest and sedated, and was constantly exhorted to sleep I found that impossible, however, because no less than forty calls were made on my attention every day

A.M.
5 00 lights on
5 10 temperature taken
5.25 blood-pressure taken
5 45 bedpans
5 55 tea
6 00 water for washing
6.30 bed made
7.30 woken by clatter from steriliser
7 45 newspaper boy
8 00 breakfast
8 40 bedpans
8.50 hand wash
9 00 sister's round
9.50 blood-pressure taken
10 00 doctor's round
10.20 drink of milk
10.25 medicines
10 45 bedpan
11 05 hand wash
11 15 shop trolley
11.25 told to get ready for weighing
11 40 weighed
11.50 asked to find tray cloth

P M
12 15 lunch
12 50 bedpans, hand wash
1.30 bed made
1 40 blood-pressure taken
2 00 medicines
2.20 physiotherapist
3 05 tea
3 40 bedpan, hand wash
4 00 temperature taken
4 40 blood-pressure taken
5 00 medicines
5 40 asked to find tray cloth
6 10 supper
6 30 bedpan, hand wash
6 35 suppository
7 00 tidying bed
7 15–8 00 visitors
8 30 blood-pressure taken
8 35 bedpan
9 00 sleeping-tablet

Some of these items did not happen every day, but others, such as blanket-baths, hair wash, and clatter of the cleaners, do not appear

Could not something be done to simplify some of the less important routine tasks? Or could not all "resting" patients be put at one end of the ward and dealt with first? Much unnecessary disturbance could be cut out in that way—such as a twenty-minute interval between setting trays and serving meals, further delay for bedpans, and delay in taking temperature and blood-pressure.

EX-PATIENT

PSYCHOSIS AND TREMOR DUE TO MECAMYLAMINE

SIR,—Dr Harington and Dr Kincaid-Smith conclude that psychosis and tremor, in their cases of hypertension, were the result of high doses of mecamylamine

It is noticeable, however, that a raised blood-urea accompanied these phenomena, and in their first case a return to normal was paralleled by a fall in the blood-urea As tremor and psychosis are symptoms of uræmia, it may not be justifiable to attribute them primarily to the effect of mecamylamine

In a case recently studied at this hospital, similar signs were present in a patient with malignant hypertension treated with only 10 mg of mecamylamine b d , and whose blood-urea ranged between 100 and 240 mg per 100 ml If this syndrome is due to mecamylamine it can be produced with doses much lower than those reported by Dr Harington and Dr Kincaid-Smith

Though Bright in his original series of papers did not describe these phenomena, Dieulafoy [1] gave the name *folie brightique* to the psychosis The occurrence of coarse tremor in uræmia is well recognised [2]

Whittington Hospital,
London, N 19
M GREENBERG
E DAVIDSON

RESISTANT STAPHYLOCOCCI IN HOSPITALS

SIR,—The most interesting article by Dr Gould and your editorial last week should induce hospitals to build two rooms especially for the use of antibiotics, one where they can be prepared under all possible precautions, and the second where they are administered That air-exhaustion plants will have to be installed is obvious, that surgical masks worn by the people handling the antibiotics will not be enough, and that something of the gas-mask type will be needed, is only too clear, and a protective cover for oral antibiotics should be demanded from the manufacturers Strictest asepsis is essential

One further point would, I believe, warrant thorough investigation It has been stated that after *one* injection of procaine penicillin traces of it can still be found in the patient 140 days later It would be interesting to examine whether these very small amounts of penicillin are concerned in the creation of resistant strains Should this be proved, then we will have to use high doses of a quickly excreted penicillin. I have been advocating this for some time—admittedly as a precaution against sensitisation

Basingstoke.
K L PETER

SIR,—There is little doubt that most hospitals are now infested with resistant staphylococci Most discussion on this subject has emphasised the role of the operating-theatre as the source of wound infection. The role of cross-infection in the wards seems to have had relatively less attention

Particularly unpleasant examples of this have recently been seen in this hospital, where there have been 3 fatal cases of postoperative staphylococcal bronchopneumonia in one surgical ward during the past two months These cases were, admittedly, poor-risk patients in a debilitated condition Apparently resistant staphylococci are commonly present in the nasopharynx of patients after a spell in hospital, and these patients had all been in hospital for some time before operation.

It seems that the weak, debilitated patient who is unable to cough adequately after a general anæsthetic may develop this fulminating bronchopneumonia, which, in our cases, failed to respond to any treatment In these circumstances it would seem to be advisable to operate on such patients as soon as possible after admission

Complete isolation of infected patients is unfortunately impractical, but, if possible, cold surgical admissions should be diverted to clean wards A much more rigid aseptic technique for dressings is needed, and the barrier-nursing principle should be used for patients with infected wounds, or resistant staphylococci in the sputum or urine Contaminated dressings should be immediately sealed in a paper bag as described by Caswell et al [3]

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[1] Aleksandrowicz, J , Spirer, L *Le Sang*, 1955, 2, 212

[2] Aleksandrowicz, J , Ostrowska A., Urbańczyk, J , Sierko, J *Blood* (in the press)

[1] *Bull Soc Méd Paris* 1885, 2, 246

[2] Combeare, J J , Mann, W N Textbook of Medicine Edinburgh, 1954

[3] Caswell H. T Schreck, K. M , Burnett, E , Carrington, E R , Leaner, N Steel H. H., Tyson, R R , Wright, W C. *Surg Gynec Obstet* 1958, 106, 1

At this hospital the wards are E M S huts heated by antiquated coke stoves The amount of dust produced by these stoves is prodigious, and I do not think that the wards can be properly cleaned unless they are closed At present, pressure of work allows this to be done only when the wards are redecorated There must be considerable accumulation of infected dust during the intervening years

This problem will surely remain with us as long as we accept a standard of accommodation and hygiene in our hospitals below that of our private houses and industry

St Peter's Hospital,
Chertsey, Surrey

Murray T Pheils

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA AND ECLAMPSIA

Sir,—Professor Browne is to be congratulated on his excellent review in your issue of Jan 18 I should like to discuss some of his points

The rise in the corticosteroid level in serum and urine argues in favour of an increased adrenal function but the chemically demonstrable corticosteroids are not the natural hormones of the adrenal, hence some caution is indicated The clinical manifestations, such as striæ and the diminished resistance to infection during pregnancy, likewise show that in pregnancy the function of the adrenal cortex is increased Few data support the hypothesis that hyperfunction of the cortex is further enhanced during toxæmia of pregnancy

In my opinion, in the pathogenesis of hypertension more attention should be paid to antidiuretic hormone (vasopressin) and sodium chloride In more than one case we have observed that administration of sodium chloride or pituitary extract can bring on a fit The uterorenal reflex [1] and the uteropituitary reflex, through which dilatation of the os uteri produces a vasopressin effect, are also factors of importance But it must be remembered that in pregnancy hypotensive substances are also formed [2-4], and the behaviour of the vascular system might be considered the resultant of two opposing forces

Increased activity of the adrenal cortex probably promotes toxæmia, but the adrenal cortex also affords a certain protection Thus, in fatal toxæmia irreversible changes (hæmorrhages and ischæmia) are often found in the hypophysis and the adrenal cortex [5 6], and cortisone is beneficial in shock accompanying toxæmia The two observations are compatible if we postulate a dysharmonious function of the adrenal cortex in toxæmia the action of the mineralocorticoids increases more than that of the glucocorticoids

The placenta fulfils its protective task only when its activity is normal In placental hypoxia numerous substances which act on blood-vessels are formed in the placenta—such as histamine, tyramine, acetylcholine, serotonin, guanidine, arginine, and thromboplastin The balance between inactivating enzymes (histaminase, monoaminooxidase, pitocinase, cholinesterase) and these substances is upset, and the vasoactive substances enter the maternal circulation

That the placenta not only exerts a protective function but also is the source of injurious substances is well illustrated by the cases in which eclampsia develops in the puerperium and placental polyps were demonstrable [7 8]

Eclampsia in the puerperium may be explained by the fact that different periods of time are needed for the development of the action of the various substances We ourselves have observed that in the first days of the puerperium the blood-pressure rises strikingly more than once We think that the substances which lower blood-pressure are excreted more quickly than those which raise it

It is necessary to emphasise the significance of the increased permeability of capillaries Eppinger [9] termed this "serous inflammation", but few obstetricians use this expression [10-12] The process explains the increase in the protein level of tissue-fluid mentioned by Professor Browne Besides the increased permeability of the capillaries the chemistry of the connective tissue also plays a part In œdema of pregnancy the skin and the subcutaneous connective tissue accumulate a substance which has the tendency to bind NaCl and water [13 14], and this property is lost on exposure to hyaluronidase Such substances are the mucopolysaccharides containing hyaluronic acid The mucopolysaccharides increase the swelling of tissues and impair the function of the organs

Vasospasm, serous inflammation, and the increased tendency of the connective tissue to swell cause hypoxia in certain parts of the brain, liver, and kidneys Injury to the cells is probably not due to oxygen deficiency alone,[10-15] but the access of nutritive substances is also made more difficult In toxæmia, different parts of the same organ (e g , the brain) may be injured by hypoxia to a different degree [13]

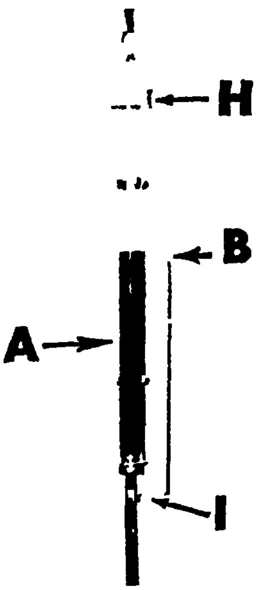
The action of the various factors (hormones and decomposition products) causing toxæmia manifests itself simply in hypoxia and impaired cell metabolism, which are reflected through their action on *different* organs, in the very variable symptoms of toxæmia

Budapest

S Fekete

A BURETTE FOR GIVING INFUSIONS TO INFANTS

Sir,—Even simpler than the apparatus described by Dr Bewes (Feb 15) is a 15 in length of 1 in outside-diameter hard-glass tubing Tubing of this bore nicely accepts the rubber bung of the National Blood Transfusion Service giving-set This makes a burette in which a change of meniscus level of 1 in represents a volume change of 10 ml The calibration is conveniently marked on a wooden base-board (B) to which the burette (A) is clipped by spring-steel tool clips (see figure)



At the start of an infusion the meniscus is brought to the zero mark by sliding the burette up or down in the clips Elaborate means of replenishment have been abandoned in favour of a "clean pour" technique The burette is detached from the base-board and held at a convenient height while the infusion fluid is poured into it from the container bottle, care being taken to avoid contact between the lips of the two vessels (In eight years of regular use we have not seen pyrogenic reactions attributable to this practice) The burette top is covered with an aluminium cap (H) which, like the glass tube, is sterilised by boiling before use The air inlet of the giving-set (redundant in this apparatus) is closed with the small cork (I) provided with the set

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1 Sophian J Toxæmias of Pregnancy London 1953
2 Shorr L , Zweifach, B W *in* Engle E T , Pregnancy Wastage Springfield Ill 1953
3 Tarján G Péteri L *Zbl Gynäk* 1955, 77, 1638
4 Péteri L , Tarján G *Gynæcologia* 1950 129 350
5 Sheehan H L *J Obstet Gynæc Brit Emp* 1939 46 218
6 Sheehan H L *Lancet*, 1948 i 1
7 Hegetschweiler, W O *Schweiz med Wschr* 1956, 86, 137
8 Moschel, R *Nervenarzt*, 1956, 27, 211
9 Eppinger, H Die Permeabilitätspathologie Vienna 1949
10 Seitz L *in* Seitz, L Amreich A J *Biologie und Pathologie des Weibes*, vol 8 Vienna 1957
11 Martius H Bickenbach W Nordmeyer, K , Droysen, K Lehrbuch der Geburtshilfe Stuttgart, 1948
12 Albers, H *Zbl Gynäk* 1944 68, 13
13 Fekete S *Acta med hung* 1954 5 293
14 Fekete S *ibid* 1957, 10 421
15 Theobald G W The Pregnancy Toxæmias or the Encymonic Atelositeses London ,1955

A burette revealing small volume changes has advantages beyond the range of pædiatrics If a three-way tap is used to connect two giving-sets in parallel, one from a litre flask the other from a burette, small volumes may be accurately introduced intermittently into a continuous infusion.

Hard-glass tubing of correct dimensions with the ends slightly belled out is supplied by Messrs R. B Turner & Co, Eagle Street London, W C I

Ipswich. R M MAYON-WHITE

ORGANISMS IN THE RESPIRATORY TRACT DURING ACUTE RESPIRATORY INFECTIONS

SIR,—We have read with great interest the excellent article by Dr Brumfitt and his colleagues [1] We have been engaged for some years in similar investigations to find the causative agent in infants and children with acute respiratory disease (bronchiolitis, bronchopneumonia, pneumonia) [2-4] Naturally we could not use bronchoscopy under general anæsthesia in infants and very young children for diagnostic purposes

The swabs examined were taken from the nose, pharynx, and larynx, by means of a sterile diphtheria stick, and from the subglottic region with a Haslinger laryngoscope by means of suction The organisms were cultured on human-blood and chocolate agar

87 infants and children with pneumonia were investigated by subglottic swabs, simultaneous throat and larynx swabs were cultured for comparison in 66 cases It was found that the subglottic swabs gave better results than the throat and larynx swab for the isolation of the supposed causative agent

We were able to isolate pneumococci, *Hæmophilus influenzæ*, monilia, and members of the *Streptococcus viridans* and neisseria groups more often from the mucosa of the throat than from the larynx and subglottis The difference in the bacterial population between the throat and subglottis was greater than that between the throat and larynx We isolated hæmolytic streptococci and staphylococci more often from the mucosa of the larynx and subglottis than from the throat (see accompanying table) Comparing throat, larynx, and subglottis swabs in the same patient, the bacterial population was identical in only 10% In 43% partial conformity was found, complete dissimilarity was never found The lower in the respiratory tract the fewer the number of saprophytes

ORGANISMS ISOLATED FROM PHARYNX, LARYNX, AND SUBGLOTTIS

Site of Swab	Pharynx	Larynx	Subglottis
No of patients	122	196	209
—	No of isolations	No of isolations	No of isolations
Pneumococcus	83 (*68%* of all patients)	113 (*58%*)	111 (*53%*)
Gram-positive cocci and *Streptococcus viridans*	105 (*86%*)	154 (*79%*)	151 (*72%*)
Gram-negative cocci	72 (*59%*)	78 (*40%*)	75 (*36%*)
Hæmolytic streptococcus	14 (*11%*)	27 (*14%*)	28 (*13%*)
Staphylococcus	6 (*5%*)	23 (*12%*)	20 (*10%*)
Hæmophilus influenzæ	6 (*5%*)	5 (*2 5%*)	6 (*3%*)
Monilia	6 (*5%*)	6 (*3%*)	1 (*0 5%*)
Sterile	6 (*5%*)	24 (*12%*)	32 (*15%*)

The bacterial population in infants and children with acute respiratory illness was not very different from that in healthy children These findings are in accordance with Adams's [5] view that with the exception of primary streptococcal infection, primary infection of the respiratory tract by bacteria is uncommon Despite this assumption he thinks that the ætiological agent should be sought by all possible means In our opinion it is possible that the different viruses can predispose the respiratory mucosa to the bacterial invasion.

It is very important to know the difference between the bacterial populations of the throat, larynx, subglottis, and lungs Since material could not be obtained from the bronchi by direct aspiration at bronchoscopy, we examined, for the sake of comparison, throat swabs, material aspirated by lung puncture immediately after death, and swabs from the lungs at necropsy

We found that where the larynx and subglottis swabs were negative, the lung swab was also negative In some cases the same micro-organism was found in the throat, larynx, subglottis, and lungs The throat and subglottis swabs usually produced mixed cultures, but in the lungs, if the swab was not sterile, there was only one organism

A potential pathogen was never found in the lung swab unless it was present in at least one other swab

B STEINER
G PUTNOKY
KLARA KOVÁCS
J SZABON

Postgraduate Medical School,
Budapest, Hungary

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[1] Brumfitt, W, Willoughby, M L N, Bromley, L L *Lancet*, 1957, ii 1306

[2] Steiner B, Putnoky, G, Kovács, K, Szabon, J *Orv Hetil* 1956 97 1189

[3] Steiner, B., Putnoky, G, Kovács, K, Szabon, J *Acta pædiat* 1958, 77 (in the press)

[4] Putnoky G, Steiner, B, Kovács, K, Szabon, J *Acta med [illegible] hungar* (in the press)

[5] Adams F H *Pediatrics*, 1957 19, 129

SEPARATION OF MOTHER AND CHILD

SIR,—Dr Bowlby (March 1) has thought it necessary to reaffirm his conviction that the separation of young children from their mother-figures is a " serious mental hazard " for many It had seemed to many readers of the investigation to which he refers [1] that he had admitted he had been wrong in believing that personality disorders *commonly* resulted when there had been an early separation trauma

He now makes two points (*a*) that during and immediately after a separation experience the majority of young children are emotionally disturbed, and (*b*) that such experiences will later on reveal themselves in serious disturbances of behaviour " in a far from negligible proportion of children "

The first point is not at issue It is sufficient in itself to enlist support for Dr Bowlby's practical recommendation that the separation of young children from their mother-figures should not be undertaken lightly

But the second point is still far from settled Dr Bowlby's own investigation is not very helpful because he treated his published data in such a way that not even a tentative conclusion can be drawn from them

His investigation was designed to compare 60 children, aged 6 to 14, who had been treated in a sanatorium before the age of 4, with a comparable control group of children in the same school classes who had not been to a sanatorium There were twice as many boys as girls in the sample, but this sex difference was largely disregarded in the evaluation of results 3 of the ex-sanatorium children were in a special school and were excluded—a mistake which was acknowledged in the paper For the remaining 57 children in the experimental sample and for their controls, observations by teachers and psychologists were available It was found that, according to the teachers' reports, no differences of behaviour existed between the two groups The outcome of comparing each item in the teachers' reports about the two groups was that, " although virtually all the differences found were adverse to the sanatorium group, none reached a level of statistical significance "

To repair this negative result, the teachers' reports were scanned for inconsistency and unreliability In the end, almost half the reports were discarded, reducing the experimental group to 32 It is obvious that such a procedure is not legitimate, for it is too easily vitiated by an understandable desire to prove the validity of a hypothesis in which one believes, rather than to test it

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[1] Bowlby, J, Ainsworth, M, Boston, M., Rosenbluth, D *Brit J med Psychol* 1956, 29, 211

There were five items in the "reliable" teachers' reports—mainly concerned with diffidence and daydreaming—which, taken together, seemed to differentiate between the two groups, but with a probability P of less than 0 001 As this unusually significant probability emerged from an effort to repair a negative result, it is likely to indicate that bias did inadvertently—though perhaps inevitably—creep into this secondary selection of acceptable reports However, there was one result, mentioned incidentally and without details, which used both reliable and unreliable teachers' reports, it was χ^2 of 13 22 for four degrees of freedom, having a probability P of 0 01 It would be helpful to have these data in full so that one could form an approximate opinion of the relative proportions of diffident and daydreaming children in the two groups

No reasons were given for the restriction of the psychologists' reports on the behaviour of children during an intelligence test to a sample of only 31 children in the ex-sanatorium group, though, according to table 4, 56 children of that group had been thus tested Surely the reliability of his teacher's report on him did not affect a child's behaviour in an intelligence test? It was not even said whether these 31 children were the same as those retained in the analysis of the teachers' reports From the small number of children included in table 9 (which compares teachers' reports and the behaviour of children in the test situation) it seems likely that they were not the same children If not, why and how were they selected?

I should be grateful to Dr Bowlby if he would publish the original figures of his investigation, so that one could judge to what extent his reaffirmed conviction is supported by the facts he collected

Maudsley Hospital,
London, S E 5

F Kräupl Taylor

A SLIDE-DRYER SLAB

Sir,—I was interested to read Dr Neumark's description of a slide-dryer slab (Feb 22) because I can claim to have devised it as far back as 1928 In 1936 the late Prof E Brumpt, of the Institut de Parasitologie, in Paris, visited this laboratory and I gave him one to take back to his laboratory

I cannot agree with Dr Neumark that wooden slabs warp Some I have, which were made in 1928, are still in use and have not warped, they were made of $^1/_2$ in teak, but oak is quite satisfactory These slabs are invaluable in laboratories where large numbers of slides have to be stained and examined—e g, in malaria surveys Mine are made to hold half a gross of slides

One of these slabs is exhibited by Colonel C A Bozman in the malaria section of the Wellcome Museum

Malaria Reference Laboratory,
Horton Hospital,
Epsom, Surrey

P G Shute

DIHYDROCODEINE

Sir,—In attempts to evaluate anileridine and dihydrocodeine as analgesic agents to supplement nitrous-oxide anæsthesia, results have been observed which differed considerably from those reported by Swerdlow [1] and by Levin [2]

Twelve patients were put to sleep with thiopentone and allowed to breathe a 50/50 mixture of nitrous oxide and oxygen When supplementation became necessary, intravenous doses of dihydrocodeine were given in amounts varying from 30 to 120 mg None of the twelve patients became quiet enough to continue the operation The one receiving 120 mg of dihydrocodeine had a severe drop in blood-pressure, which was alleviated by the use of ephedrine All twenty-six patients given anileridine under similar circumstances were anæsthetised adequately for continuance of the operation

University of Colorado
Medical Center,
Denver, Colorado

Robert W Virtue
Kathleen W Payne

A BROAD VIEW OF CANCER

Sir,—Your mention of Sir Wilfrid Le Gros Clark's opinion that speculations are of great value as a basis for experiment [1] encourages me to put forward a working hypothesis about carcinogenesis which I elaborated during my research at the University of Lwów in Poland before the late war

In my work on blood coagulation, I used as thromboplastin watery extracts of different tissues, mostly lungs, which I obtained by grinding the normal tissue with physiological saline solution and removing the remaining solid parts by centrifuging An extract of malignant tissue, prepared in the same way, showed no thromboplastic action I repeated the experiment with five different malignant tissues, none had any thromboplastic action

Dr Julian Huxley [2] has said that cancer research can only prosper if it is broadly based My working hypothesis is on a very broad biological basis

The smaller content (or even absence) of thromboplastin in malignant tissues seems to have some connection with the so-called organising capacity of normal tissues This was first discovered by Speemann, who found that the dorsal lip of the blastopore of a newt gastrula can induce the development of a new dorsal plate when inoculated between the entoderm and ectoderm of the same or another gastrula of the newt This property was called by him "organising capacity", and the part of the gastrula that was the carrier of this property the "organising centre"

Later it was found that this property was not connected with the cellular structure of the organising centre, and Holtfreter found evidence of it in all animal tissues Inducing capacity becomes much stronger when the tissue is boiled before inoculation, and its strength increases with the phylogenetic development of the donor, thus, it is strongest in man No inducing capacity has been found in plants

On the other hand, all animal tissues contain thromboplastin The content of thromboplastin is proportional to the phylogenetic development of the animal and ontogenetic development of the organ concerned The highest thromboplastin content is in organs incapable of regeneration (e g, lungs and brain) The thromboplastin obtained from the lungs of a rabbit acts more strongly on rabbit than on human blood, but thromboplastin from human placenta acts as strongly on rabbit as on human blood Thromboplastin, unlike inducing factor, is thermolabile Moreover, boiled-organ extracts show the presence of a coagulation-inhibiting substance (perhaps heparin)

Thus the two factors are in some sense antagonistic, because the destruction of thromboplastin by heat increases the action of the inducing factor, moreover embryonic organs contain less thromboplastin than the organs of fully developed animal, or none at all, and the inducing capacity of the organs of the newt embryo decreases parallel to the development

The function of the coagulation mechanisms of blood, besides preventing loss of blood from the vessels, is the repair of damage suffered by the body The wound is filled with blood, which coagulates under the influence of the thromboplastin from the tissues, the fibrin fibrils serve as a substratum for the growth of fibroblasts, which later form the scar Thus the coagulation of blood in the tissue is the first step in repair, and can be regarded as a constructive process, which is initiated by thromboplastin

The organising or inducing agent seems to be rather an agent of growth The process of gastrulation seems to have two components—growth and construction The essence of gastrulation and primordial development seems to be the vigorous growth and division of cells, initiated in normal newt embryo by a substance present in the dorsal lip of the blastopore The arrangement of the new cells in primitive organs probably depends on another factor, a constructive one, present in all cells of the gastrula

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[1] Swerdlow, M *Lancet*, 1957, i, 482.
[2] Levin J *ibid* 1957, ii, 338

[1] See *Lancet*, 1957, ii 728
[2] *Ibid*, p 837

There is thus some basis for supposing that each tissue contains two agents, of growth and of construction, which are in some kind of equilibrium As long as this equilibrium is maintained, the behaviour of tissues, organs, and the whole body is normal, as soon as it is disturbed, the behaviour of tissues becomes abnormal, and the result is a tumour

For example, in the skin, the basal-cell layer of the epidermis is probably a permanent carrier of the agent of growth, as its cells are continually dividing and delivering material for the upper layers The papillary layer of the dermis is probably the main carrier of the constructive agent, which keeps the ever-regenerating epidermis in order and prevents the ingrowth of its cells into the dermis This can be deduced from the anatomical structure of papillomas, which are very often the precursors of carcinomas The enlarged ridges of dermis to which the normal papillæ are modified, suggest that the dermis has to resist, and is still resisting, the increasing pressure of excessively growing epidermis When this resistance is broken the epithlial cells start to grow into the dermis, thus becoming malignant cells This anatomical picture permits the supposition that the mode of action of constructive agent is the checking and control of growth, and that in the normal organism both these agents are in balance Thus a factor which damages the basal-cell layer may disturb the relations between epidermis and dermis If the damage is transient, these relations can be restored, but if the damage is permanent—e g , those inflicted by carcinogens or by chronic injuries which prevent the return to normal conditions—the disturbance is permanent If the papillary layer still contains enough constructive agent to check the excessive growth of epidermal cells, nothing visible will happen But if the papillary layer should be damaged (as in the experiments of Deelmann [3]) the action of its constructive agent would be impaired, and a "crop of papillomas" might result

Again, sarcoma is commoner in young than in older persons As the natural growth in young individuals is not yet finished, many different cells still have the tendency to division, and the situation described above is possible for all of them In older persons, only epithelial and glandular cells grow Thus the processes I have described can arise only in connection with these cells The capacity of healing wounds is greatly diminished in older persons, suggesting that the function, and perhaps even the amount, of constructive agent in the tissues is diminished

Thus we can explain the long latent periods between the application of carcinogens and the emergence of tumours When the constructive agent in the dermis becomes impaired by the carcinogen, the dependence of the epidermal cells on the dermis becomes less, and the less dependent these cells become on the substratum, the greater is the chance of their survival and reproduction

In this manner over a period of time (latent period), during which also the constructive agent in the dermis is diminishing with the ageing of the organism, a form of natural selection takes place, and finally cells are produced which are completely independent of the substratum and thus autonomous—i e , malignant cells are formed

This is consistent with a greater incidence of cancer in older people.

Unfortunately since the war I have been unable to test this hypothesis experimentally

Crossley Hospital
Frodsham, Warrington, Lancs.
H Z E SCHEURING

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[3] *ibid* p 779

GLUCOSE-TOLERANCE TESTS

SIR,—Interest has recently been renewed in the intravenous glucose-tolerance (I V G T) test, since by suitable mathematical treatment of its data a numerical index of glucose tolerance can be obtained Unfortunately, the usefulness of the test is marred by disagreement concerning its underlying physiological mechanisms, so that two mutually incompatible indices are now in use

In this country the "increment" index (calculated from the slope of the straight line obtained by plotting against time the logarithm of the height of the blood-glucose concentration above fasting level) is regarded as the more valid,[1] since Duncan [2] and Baird and Duncan [3] have published the results of well-planned investigations in its favour But elsewhere the "total" index (obtained from the slope of the straight line obtained by plotting log "total" blood-glucose against time) is preferred

My purpose is firstly to draw attention to the strong arguments of Ikkos and Luft [4] in favour of the "total" index, and secondly to suggest explanations other than the inconstancy (and hence the invalidity) of the "total" index for the results obtained by Duncan [2] and Baird and Duncan [3]

The difference between the two views seems to arise from different assumptions concerning the time needed for injected glucose to diffuse throughout the glucose space The loss of injected glucose from the vascular system by diffusion is at first extremely rapid, which may be why Duncan and others have assumed that it is complete within a few minutes However, the rate of diffusion is governed by the difference in glucose concentration between plasma and extracellular water, so that, though at first rapid, it becomes progressively slower as this difference diminishes From a statistical analysis of one hundred and seven I V G T curves (following glucose 25 g given intravenously within 2–3 minutes) Ikkos and Luft [4] claim that diffusion is an important distorting factor for 25–30 minutes from the beginning of injection, and this order of time is supported by various observations in studies using radioactive glucose, and by the diffusion-time of substances other than glucose In tests using glucose 25 g , a linear relationship with time after the 1st 25–30 min is given by log "total" blood-glucose but not by log. glucose "increment" (whatever data are examined), and this dependence of the rate of glucose utilisation upon total glucose content agrees with observations of the rate of utilisation during fasting (when utilisation is balanced by hepatic glucose secretion) and after hepatectomy [4]

Now a possible explanation of the increase in the "total" index with increase in glucose load (from 25 to 50 g) observed by Duncan [2] is that the larger load requires a longer time to diffuse throughout the glucose space In Duncan's I V G T tests, blood samples were taken for 70 min , but at only 10 min intervals after 30 min , and while this procedure gives sufficient data with a 25 g load, it provides few data for the critical tail ends of the curves obtained with 50 g Nevertheless, if regression coefficients are calculated for log mean values of the data for a 25 g load after 20 min (i e., 27 min after the start of the injection), and of the data for 50 g after 30 min , and the differences tested against their standard deviations, the difference in slope at the two load levels is not significant in the normal group (P>0 05), and is significant at the 0 01 level for the mildly diabetic group There is therefore considerable uncertainty as to whether increase in glucose load does in fact change the "total" index, more frequent sampling after 30 min and extending beyond 70 min is needed to settle the matter

When Baird and Duncan's data [3] on mild diabetes before and after treatment with carbutamide are similarly examined statistically (using values after 27 min), the difference in the regression coefficients is significant ($P < 0\,001$), in terms of the total index, the value is increased by treatment from 0 47 to 0 69% per min, the higher value remaining, however, within the diabetic range The mode of action of carbutamide is still uncertain, and it is difficult to accept data from oral-glucose-tolerance tests and the daily fluctuations in blood glucose as proof of the absence of small differences in glucose utilisation, the apparent inconstancy of the "total" index may therefore reflect a real change in rate of utilisation—an observation of some interest

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[1] *Lancet*, 1957, ii, 33
[2] Duncan, L J P *Quart J exp Physiol* 1956, 41, 85
[3] Baird, J D , Duncan, L. J P *Clin Sci* 1957, 16, 147
[4] Ikkos, D , Luft, R. *Acta endocr , Copenhagen*, 1957, 25, 312

Research Department, Runwell Hospital,
Wickford, Essex
I G PRYCE

INCIDENCE OF WOUND INFECTION

SIR,—In the study recorded in their article of Feb 15 Mr Jeffrey and Mr Sklaroff found a much higher incidence of wound infection in general surgical cases than in orthopædic and neurosurgical cases Among the possible factors contributing to this difference they did not consider suture material It is likely that the practice in Edinburgh is that found in most centres—i e, that orthopædic surgeons and neurosurgeons use little or no catgut in wounds while general surgeons use a great deal Of the many studies which have shown the effect of catgut in wounds one of the most striking was that by Jones et al[1] who reduced the incidence of wound infection in the abdominal wounds after abdominoperineal resections of the rectum from 27 5% to 0 85% by substituting alloy steel wire for catgut in the peritoneal and muscle layers When the catgut was only partially replaced by wire the rate of wound infection lay between these two extremes

From my own observations I agree with Jeffrey and Sklaroff that the contamination of wounds occurs usually in the operating-theatre, and the above-mentioned study indicates that the presence of dead animal tissue, in the form of catgut, allows the organisms to establish an obvious wound infection much more readily than they do when catgut is absent

Manchester
HERBERT HAXTON

MYOCARDIAL INFARCTION AND TRANSIENT GLYCOSURIA

SIR,—Dr Rees, in his interesting article on accidental hypothermia (March 15), ascribes the occurrence of hyperglycæmia and glycosuria noted in case 2 to hypothermia I wish to take the opportunity to point out that transient glycosuria is a common complication of myocardial infarction—a fact which does not appear to be widely appreciated Thus, the association is not mentioned in standard textbooks of medicine, and is ignored by most textbooks of cardiology

Scherf[2] described the association in 5 cases collected over a period of eight months, and estimated the frequency at 10% During the past two years the association was found in 12 patients in a consecutive series of 129 cases of proven myocardial infarction admitted to a general medicine unit, where the patient had been seen within forty-eight hours of the onset and where the urine had been tested (a further 12 patients had myocardial infarction complicating diabetes mellitus) This series suffers from bias in several respects and is probably not representative nevertheless there is no doubt that this is a common phenomenon The ætiology is not understood, though Scherf advances several interesting hypotheses

This is an aspect of myocardial infarction which appears to have been neglected and which might repay fuller study

The Royal Infirmary,
Edinburgh
J KNOX

MEMORIAL TO SIR JOHN GRAHAM KERR

Lord BOYD ORR writes

"A committee has been formed for the promotion of a fund to commemorate the late Sir John Graham Kerr who occupied the chair of zoology at Glasgow University from 1902 to 1935 Many medical graduates of Glasgow will remember with affection and respect the distinguished and congenial professor they met in the first year of their studies Those who wish to be associated with the memorial should send a contribution, however small, to Miss A E Miller, Department of Zoology, The University, Glasgow, W 2"

Parliament

Children Bill

THIS Bill, which was read a second time in the House of Lords on March 11, deals with the welfare and protection of foster children and adopted children

The first part, which covers foster children, consolidates and modifies the present law It lays on local authorities a more positive duty to ensure the wellbeing of these children and gives it new powers to help it to do so

A local authority, for instance, is empowered to prohibit a child being received in an unsuitable home, it must arrange that foster children within its area are visited, its officers are entitled to inspect premises in which foster children are to be kept or are being kept and may make requirements about the medical arrangements, and it may also remove a child from an unsuitable home

The second part of the Bill, which covers adopted children, is based on the main recommendations of the Hurst report[1] and VISCOUNT KILMUIR, the Lord Chancellor, in his opening speech said that many of the recommendations which did not find a place in the Bill would be implemented by means of rules and regulations

One of the important changes which the Bill makes is to provide a further ground on which the court may dispense with the consent of a parent to an adoption of a child The proper balance between the best interests of the child and the rights of the natural parent was, Lord Kilmuir said, often very difficult to obtain Adoption was not a case in which the welfare of the child could be the sole and paramount consideration the courts must consider also the reasonable wishes of the natural parent But there were occasional cases in which a parent had for long shown no sign of carrying out the ordinary responsibilities of a parent and no sign of any intention to do so, yet nevertheless refused to consent to an adoption which would in every way be in the interests of the child The Bill provided that a court might dispense with the consent of the parent when the parent had persistently failed, without reasonable cause, and when that parent seemed likely to continue to do so if the adoption order was not made

Other provisions of the Bill extend the circumstances in which an adopted child is treated as a child of the family for the purposes of succession to property and in which a child, under safeguards, may be taken abroad for adoption This last provision should enable more coloured children and more Catholic children to find adopting families

The only important recommendation of the Hurst Committee which the Government have not accepted is the recommendation that in England and Wales an adopted person on reaching the age of 21 should have the right to be told the names of his natural parents (In Scotland he is able to do so at the age of 17, in England only at the order of a court of competent jurisdiction) As this proposed innovation had caused anxiety to some of those with great experience of adoption, the Government, Lord Kilmuir said, had decided to leave the law as it stood both in England and Wales and in Scotland

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[1] Jones T I, Newell E T, Brubaker R E *Surg Gynec Obstet* 1941, 72, 1056

[2] Scherf D *Wien klin Wschr* 1933, 46, 69

[1] See *Lancet*, 1954, ii, 710

QUESTION TIME

Shortage of Psychiatrists

Mr KENNETH ROBINSON asked the Minister of Health how many psychiatrists of each grade, in whole-time equivalents, were in post in the mental hospitals of England and Wales —Mr WALKER-SMITH The following were the figures in 1956

—	Mental illness departments	Mental deficiency departments
No of patients in residence	150,984	53,519
Medical staff in post in whole-time equivalents	1330	205
Consultants	423	66
S.H.M O s	276	54
Senior registrars	101	5
Registrars	218	23
J H.M O.s	217	53
Senior house-officers	95	4

Mr ROBINSON Will the Minister initiate discussions with the teaching hospitals, the Royal Colleges, and the Institute of Psychiatry on the urgent need to train more psychiatrists ?—Mr WALKER-SMITH The question whether there is a need for more training posts in psychiatry and other specialties will shortly be discussed with representatives of the profession

Mr ROBINSON Will the Minister agree that the key to this serious shortage of psychiatrists lies in the teaching hospitals, and that some initiative will have to be made, probably by himself and his Department, in order to overcome the highly conservative nature of medical curricula in this respect ?—Mr WALKER-SMITH I would not like to take an unduly pessimistic view of this matter I am glad to say that the intake to the senior registrar grade in psychiatry is actually larger than to any other specialty, and has recently been further increased There has also been a substantial increase in the number of registrars to the extent of 39% between 1953 and 1956

Sale of Amyl Nitrite

Captain H B KERBY asked the Secretary of State for the Home Department if he would prohibit the sale, without a doctor's prescription, of vitrella amyl nitrite, a stimulant drug, now widely peddled and used by prostitutes, procurers, and other members of the organised vice racket in the West End of London and elsewhere, and if he would make it a criminal offence for anyone, other than a doctor, to administer this drug, bearing in mind that it undermines moral resistance and is the first step to drug addiction —Mr R A BUTLER replied Amyl nitrite is controlled as a poison, but the Poisons Board has not in the past considered that there was sufficient evidence of its abuse to warrant the application to it of the stricter controls which apply to the more dangerous poisons I am, however, keeping the matter under close review

Cost of Pharmaceutical Preparations

The price index for all manufactured products—other than fuel, food, and tobacco—was 41 6% higher for January, 1958, than at June 30, 1949 Over the same period the index for drugs and pharmaceuticals has risen by 6 6%

General Practice

The number of principals, assistants, and trainees in general practice in England and Wales in 1952 and in 1956 was as follows

—	July 1, 1952	July 1, 1956
Principals—single-handed	7459	6568
Principals in partnerships	9745	12 514
Assistants	1689	1546
Trainees	309	368
Total	19,202	20 996

Medicine and the Law

Fatal Agranulocytosis due to Novalgin

AN open verdict was recorded on March 12 at a Colchester inquest on a man, aged 57 [1]

He had had an accident in 1945 and had not worked since, he had much pain, for which phenobarbitone and 'Novalgin', a proprietary drug derived from amidopyrine, were prescribed—first in hospital, and later by his family doctor Six months before death he had had an infection of the mouth, which seemed to clear up, then recurred Novalgin was continued, and despite antibiotic treatment he died of bronchopneumonia two days after admission to hospital A pathologist at the hospital said that the patient had agranulocytosis The coroner asked the family doctor whether he suspected that novalgin was causing the agranulocytosis, and he replied "He had been on it so long that I don't think it made any difference I really did not think very much of the novalgin drug" A director of the firm manufacturing novalgin said that he knew of only 12 cases of agranulocytosis from the drug since 1926, with 2 or 3 fatalities It was marketed purely because there were a small group of people to whom it gave relief when other compounds were unable to do so

The coroner said that verdicts of accidental death or death from natural causes would be inappropriate, because "the start of the cause of death" was the administration of novalgin.

At a meeting of the Association of Clinical Pathologists in 1951,[2] it was pointed out that amidopyrine was sold under very many trade names, and a doctor might not always know when he was prescribing it Dr George Discombe had seen 4 fatal cases and estimated that the incidence of agranulocytosis was about 1% in those taking amidopyrine

Child's Death after Nibbling Paint

A boy, aged 2, was given to nibbling the painted window-sills at his home, though his mother "had taken steps to correct him" [3] He vomited "a large ball of paint", but died in hospital of lead poisoning At an inquest, in Norwich, a verdict was recorded of death by misadventure

Lonely Old People

Dr D W Browne has said that it is one of the saddest of his duties as medical officer of health to move old people against their wishes to institutions [4] Despite need of hospital care, which is obvious to others, they often insist on remaining at home The first application for compulsory removal in Argyll was lately made in the case of a woman, aged 83, with a probable fracture of the hip [5] She lay helpless in her croft without heat or food Since her accident the livestock of the croft had been disposed of, there was no water in the house Neighbours did their best, but she seemed to be living mainly on cups of tea. Yet she refused to go into hospital, and, with the approval of her relations, the Sheriff has ordered her compulsory removal to the Western Infirmary, Glasgow

The married are apt to fare better in hard times when they grow old, but tragedies are still possible A bedridden man, aged about 80, is thought to have starved to death over the course of a fortnight in a Gorbals, Glasgow, flat, after his wife died[6] Receiving no answer, neighbours called the police, who forced the door and found the husband, who had been an invalid, dead in bed for lack of food and drink, and his wife, who had died from natural causes, lying on the floor nearby It was thought that the husband had died about 2 days before, and the wife a fortnight earlier

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[1] *East Anglian Times*, March 13, 1958
[2] See *Lancet*, 1951, i, 389
[3] *Birmingham Post* March 13
[4] See *Lancet*, 1957, i 1002
[5] *Scotsman* March 12

Obituary

RUBY OLIVE STERN

M D Lond

Dr Stern (Mrs Horton), formerly pathologist to St Andrew's Hospital, Northampton, died at Northampton on March 13 at the age of 56

She was born in London and educated at Queen's College, Harley Street, and Charing Cross Hospital She qualified in 1925 and took the M D Lond in pathology in 1932 After holding the post of demonstrator in pathology at Charing Cross she worked for some years with the late Dr J G Greenfield on neuropathology at the National Hospital for Nervous Diseases, Queen Square, and published papers in *Brain* on infantile muscular atrophy, the histopathology of tabes dorsalis, and aspects of neurosyphilis She was next appointed Sébag Montefiore research fellow and morbid anatomist to the Hospital for Sick Children, Great Ormond Street, and two years later became pathologist to St Andrew's (Mental) Hospital, Northampton On her marriage in 1938 she resigned her appointment at St Andrew's Hospital, during the late war, however, she began to work in an honorary capacity in the pathological department of Northampton General Hospital, and continued to do so until her health began to fail Her last scientific paper was published in the *British Journal of Cancer* in 1954, on the morbid anatomy of carcinoma of the bronchus At the time of her death she was honorary secretary of the local committee of the British Empire Cancer Campaign, and was assisting with the records of the radiotherapy department of Northampton General Hospital

A colleague writes

Olive Stern had a brilliant and well-cultivated brain, but in mid-career she gave up the scientific promise of her early years in neuropathology for a happy married life that lasted for seventeen years Her husband, a well-known Northampton manufacturer, died three years ago

FRANK KELLETT

M A, M B Cantab

Dr Frank Kellett, director of a pathology laboratory in Harley Street, London, and pathologist to the Hospital of St John and St Elizabeth, died on Feb 27 at the age of 55

He was born near Dewsbury, Yorks, and studied medicine at Christ's College, Cambridge, and St George's Hospital, qualifying in 1927 He started work in Harley Street in 1928 and was appointed pathologist to the Hospital of St John and St. Elizabeth in 1931 He was a member of Gray's Inn He leaves a widow and a son

H S W writes

Frank Kellett was a pathologist of wide experience and high technical skill He was a true enthusiast, willing to take endless pains to assist clinicians in solving their diagnostic problems His insistence on rigorous technique and checking of results went a long way to establish his reputation for reliability As a friend and colleague, with his characteristic sense of responsibility, he was invariably loyal and helpful He possessed a strong sense of humour and a sharp wit which he directed against the follies and pomposities of the world Although in ill health for the last few years, he steadfastly continued with his work

Dr J. G GREENFIELD

S C D sends the following tribute to Dr Greenfiel work for the Association of Clinical Pathologists

Greenfield warmly welcomed the suggestion to form association and he attended the meeting in 1927 at which was first publicly discussed and he seconded the motion whi brought the Association into being At that meeting he w elected to the council of the newly formed Association Fr 1928 to 1933 he was vice-president and chairman of coun and from 1934 to 1937 president, and he continued serve as a member of council till 1942 He served on t editorial board of the *Journal of Clinical Pathology* from 19 to 1957

It was largely owing to his influence throughout these yea that the association gave increasing attention and effort educational measures designed to produce a race of patholog capable of playing their full part in the development of clini medicine In November, 1927, he was one of the represent tives who put the views of the Association before the board the faculty of medicine of the University of London in interview which led to the establishment, in 1929, of t diploma in clinical pathology by the university In 19 Greenfield was elected an honorary member of the Associatio and the same year he gave the Foundation lecture in which reviewed the clinical pathology of encephalomyelitis T Association has lost a counsellor whose words were alwa wise, temperate, and at the same time authoritative

Diary of the Week

MARCH 23 TO 29

Monday 24th

MANCHESTER MEDICAL SOCIETY
9 P M *General Practice* (Medical School, University of Mancheste Mr Richard Johnson Neurosurgical Conditions in Gener Practice

Tuesday, 25th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr J G Scadding, Dr Philip Ellman, Dr A Heppleston The Lungs as an Index of Systemic Disease

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
5 30 P M Dr Imrich Friedmann Role of Tissue Culture and Electron microscopy in the Study of the Ear

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Stree W 1
5 30 P M Dr G A D Gordon Neuroradiology

Thursday, 27th

ROYAL SOCIETY OF MEDICINE
8 P M *Neurology* Dr W B Matthews, Dr R T C Pratt, Dr Harr Harris Clinical, Genetic, and Biochemical Disorders of th Nervous System
8 P M *Urology* Mr G F Murnaghan, Mr Howard G Hanley Mr F R Raper, Mr D Innes Williams Lower Third of Ureter

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, E C 4
5 P M Mr C Naunton Morgan *Non malignant* Diseases of the Colon
6 15 P M Mr A W Badenoch Genito-urinary Tuberculosis

Friday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln's Inn Fields, W C 2
4 30 P M Sir Stewart Duke Elder Emergence of Vision in the Animal World (Lister oration)

ROYAL SOCIETY OF MEDICINE
8 P M *Obstetrics and Gynæcology* Prof T N A Jeffcoate Culdoscopy Mr J S Scott, Dr A D Bain Amnion Nodosum Mr H H Francis Pregnancy and Addison's Disease

SOCIETY OF APOTHECARIES OF LONDON
5 P M Sir Charles Dodds Endocrine Therapy in Surgery
6 15 P M Mr Rodney Maingot Splenectomy

MEDICAL RESEARCH COUNCIL
5 P M (National Institute for Medical Research Mill Hill N W 7) Prof N I Kalabukhov (Saratov, U S S R.) Seasonal Changes in the Organism of Mammals in Relation to the Environment

BRITISH TUBERCULOSIS ASSOCIATION
11 15 A M (Department of Zoology, University of Cambridge) Dr M C S Kennedy Mr O S Tubbs Dr W F Lloyd Uncommon Diseases in the Lung (Opening of two-day meeting)

Saturday, 29th

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES
2 P M (Manchester Royal Infirmary Manchester) Dr A N Ashworth Results of Local Treatment of Interstitial Keratitis with Cortisone Prof J H Kellgren Differential Diagnosis of Reiter's Syndrome

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[6] *Times*, March 1

Notes and News

NEW EYE HOSPITAL IN JORDAN

"One of the greatest things ever done by the Order of the Hospital of St John of Jerusalem" is the new ophthalmic hospital now being built near Jerusalem on the Jordan side. This was the phrase used by Sir Stewart Duke-Elder in a lecture last Monday on the Past, Present, and Future of the Ophthalmic Hospital, Jerusalem. A hospital was established in Jerusalem as long ago as 600 A.D. It was rebuilt in 800 by Charlemagne, who added a library, but was rased (with the rest of Jerusalem) in 1009. The hospital was rebuilt in 1070 and used during the Crusades both as a war hospital and for the relief of the local inhabitants. The Order was founded to serve "our lords the sick", Saladin offered a free passage to its members when he pushed the Crusaders back to Acre, but they stayed with the wounded.

The hospital, like the Order, survived many vicissitudes through the centuries. In 1917 it was used as an ammunition dump by the Turks and blown up, it was rebuilt in 1918 as an ophthalmic hospital, to become, in Sir Stewart's phrase, a "showplace of the Middle East". But during the Arab-Israeli war of 1948 it was again a stronghold, and at the armistice the Israel-Jordan demarcation line ran through the garden of the ruined hospital. Lord Webb-Johnson restarted the hospital in two houses in the old city of Jerusalem, on the Jordan side—houses reached by a road which is also a stairway. It serves not only the 500,000 refugees and the 1,500,000 population of Jordan, but the whole Middle East, and it is entirely a charity.

Sir Stewart then turned to the new hospital which the Order is now building. The 150,000 patients seen at the present hospital in 1957 are but "a drop in the bucket", and the new buildings will comprise a much larger hospital and nurses' home, a postgraduate medical school, and laboratories particularly for research into trachoma, which causes a quarter of the world's blindness. The laboratory has been built for two years, and the nurses' home will be ready in a few weeks, when the main building will be started, occupation should be complete in two and a half years. All nations in the Middle East have cooperated freely in this great enterprise.

MENTAL HEALTH RESEARCH FUND

In the year ended Sept 30, 1957, the Mental Health Research Fund allotted £19,914 to research projects (which ranged from social and educational to biochemical and electrocardiographic investigations) and to grants enabling workers to attend conferences abroad. The Fund has organised an international conference to be held in Oxford in July. Its object will be to elucidate and relate to each other the various uses of the concept of stress in psychiatry and physiology.

A NEW PHARMACOPŒIA

A NEW edition has appeared of the *St Thomas' Hospital Pharmacopœia and Vade Mecum*, compiled by Dr J B Harman and Dr R S Stacey. It lists drugs and preparations in alphabetical order, with entries under the approved names and cross-references under other names. Each entry gives a brief account of the actions of the drug, its dose, and the preparations available. There are lists of drugs under such headings as Antibiotics and Hypnotics. At the back are 60 pages of terse information on subjects ranging from biochemical normals to tables of life expectancy. The pharmacopœia, which should be invaluable to any clinician, may be obtained from the secretary, St. Thomas's Hospital, London, S E 1, for 9*s* post free.

A NEW HÆMATOLOGICAL JOURNAL

Dr William Dameshek, editor of *Blood*, lists 19 periodicals currently devoted to hæmatological subjects.[1] This number includes *Hæmatologica Cracoviensis*, a new clinical quarterly.[2] The first two numbers contain articles in Polish with Latin summaries, but Prof Julian Aleksandrowicz, the editor, states that articles in other languages will be accepted. Polish is no easy language, and Latin is now a disappearing requirement for medical students. We respectfully suggest that a fairly long "summario in interlingua", which is readily understood, would be widely welcomed. We should all like to learn the views of our Polish colleagues on current problems.

MEDICAL FILM

Selected Immunisation Techniques (16 mm, sound, colour, 33 min, Great Britain, 1956) is an Air Ministry film, designed primarily for R.A.F. medical personnel, dealing with sensitivity tests and active immunisation.

The film opens with a diagram of the skin in section, and the thickness of the underlying tissues in different parts of the body is compared. Sites for immunisation and sensitivity tests are discussed and the preparation of the skin, the patient, and the instruments is shown in detail. The middle third of the film demonstrates immunisation techniques including scarification, multiple pressure, intradermal, subcutaneous, and intramuscular injections. Finally Schick testing is shown, and vaccination by the scratch and multiple-pressure methods is demonstrated in detail. Typical skin reactions are compared.

This long film is packed with information. The film falls into three almost equal parts, and if these were issued separately, each concluding with a summary, they would be valuable for undergraduate teaching. The colour photography, animated diagrams, and commentary are of a high standard, and the slow-motion sequence showing needles entering the skin as a result of good and bad injection techniques is excellent.

Copies are obtainable on hire from the Air Ministry, S T 4, Richmond Terrace, London, S W 1.

University of Cambridge

On March 8 the following degrees were conferred.

M D—M H. S Bound, P J Crowley, P E. Hughesdon, K J Martin.
M S—R. G Beard.
M.B., B Chir—D S Filer (by proxy).
M.B—J G Miller, C S Goodwin.

University of London

On Feb 26 the following degrees were conferred.

M.D—Derrick Jackson.
M S—B H Hand.

University of Birmingham

Prof E C Amoroso will deliver the Ingleby lectures on Thursday and Friday, May 1 and 2. Prof J S Mitchell will give the William Withering lectures on Tuesday, Wednesday, and Thursday, May 13, 14, and 15. All the lectures will be given at 4 P.M. in the large anatomy theatre of the medical school.

University of Liverpool

The North Western Area Cancer Research Fund general committee of the Friends of Liverpool Radium Institute are to give £50,000 from their funds to the university to finance a new unit to investigate endocrine factors in cancer (*Liverpool Daily Post*, March 13). The use of the funds of the Friends has been the subject of legal proceedings and the Attorney General of the Duchy of Lancaster has to approve the gift.

University of Edinburgh

On July 3 the honorary degree of LL.D will be conferred on Prof F A. E Crew.

Institute of Diseases of the Chest, London

Clinical demonstrations will be arranged by Dr J G Scadding at the Institute, Brompton Hospital, S W 3, at 5 P.M. on Fridays from April 18 to July 4. There will be open lectures at 5 P.M. on Wednesdays from April 23 to July 2.

North of England Otolaryngological Society

The prize (50 guineas) of this society has been awarded to Dr A E Gregson of Leeds for his essay on acute osteomyelitis of the maxilla in infants. Mr J H Otty has been elected president and Mr R. M. Marshall vice-president.

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[1] *Blood* 1958, 13 83.
[2] The editorial and administrative office is at III, Klinika Chorób Wewn Kraków, Kopernika 17, Poland.

Royal College of Surgeons of England

At a meeting of the council on March 13, with Sir James Paterson Ross, the president, in the chair, Prof Clarence Crafoord was admitted to the honorary fellowship Mr William Gissane was appointed a Sir Arthur Sims Commonwealth travelling professor to visit Australia in 1959

A diploma of membership was awarded to G M Makhlouf

Faculty of Anæsthetists—Dr R P Harbord has been elected member of the board for eight years

The monthly college dinners will be held during 1958 on Wednesdays, April 16, May 7, June 11, Oct 8, Nov 12, and Dec 10

The following are eligible to attend with their wives and guests fellows of the college, members of the college, fellows and licentiates in dental surgery, fellows and members of the Faculty of Anæsthetists, holders of special diplomas, students of the college, and members of associations linked to the college through the joint secretariat Applications for tickets (£1 10*s*) should be sent to Mr W F Davis, the deputy secretary of the college, Lincoln's Inn Fields, London, W C 2.

Society of Apothecaries of London

At recent examinations the following were successful

M M S A—D P C Chan, R Ratnaraj

L M S S A—L C T van Oudenhove de St Gery, J Rivers-Kirby, F A Rashid El Lamki, J G Miller, B S Mather, L Manoharan M Kiloh, B M Allen, P J Bishop, B J P Hall, J M Mokuena, K K Yong, G J Evans, J G Wright, J G D Simpson, J T Aroney, P J Gladders, G R Hill, F G de L Wright, J F R Adams, D H Barham, G F D Heseltine, B J Horgan, R H MacKeith, D R Pershad

D I H—D F Bedford, D M Lewis, H R Mallows, S K Sen

Grants for Psychiatric Research

The Foundations' Fund For Research in Psychiatry is offering block grants ($3000–$12,000 for up to five years) to departments of psychiatry in medical schools to stimulate research and teaching Further particulars may be had from Dr Max M Levin, the executive officer of the fund, 251, Edwards Street, New Haven 11, Connecticut

Association of Industrial Medical Officers

A meeting of this association will be held at the London School of Hygiene and Tropical Medicine, Keppel Street, W C 1, on Friday, March 28, at 10 A M and at St George's Hospital, S W 1, on Saturday, March 29, at 10 A M The speakers will be Mr J D Cameron, Dr J C Graham, Dr P A B Raffle, Mr Rowden Foote, Squadron-Leader Peter Howard, Sir Harold Whittingham, and Mr H Elliott Blake

National Association for the Prevention of Tuberculosis

On Thursday, April 24, at 3 30 P M at the Royal Victoria Infirmary, Newcastle upon Tyne, this association is to hold a symposium on chronic bronchitis The speakers will be Dr A G Ogilvie, Dr C M Fletcher, Mr Alan Johnstone, Miss Lynne Reid, Dr J R May, Dr P O Leggat, Dr R C Browne, Dr D D Reid, and Dr C W Bartley Tickets (10*s*) may be had from the association, Tavistock House North, London, W C 1

The Cambridge House Show

Cambridge House is midway between Camberwell Green and the "Elephant", and must seem remote from Trinity College, Cambridge Yet Trinity Court was begun there in 1889 by Trinity men, and was succeeded by Cambridge House, which is one of the oldest of the university settlements The president is Lord Tedder Its activities include a community association, boys' clubs, an old people's club, and a legal advice centre, it is supported by several Cambridge colleges, besides the London County Council, several companies, and private subscription.

A variety show is to be held, in aid of the funds of the settlement, at the Commodore Cinema, Hammersmith, on Sunday, March 23, at 7 P M Tickets (3*s* 6*d* to 12*s* 6*d*) may be had from the cinema, or from the secretary, Cambridge House, 131, Camberwell Road, London, S E 5

Malaria Therapy

Requests for material for the infection of patients requiring malariatherapy should continue to be addressed to the director of the Malaria Reference Laboratory, Horton Hospital, Epsom, and not to the London or Liverpool schools of tropical medicine

Society for the Study of Fertility

On Wednesday, April 9, at 5 P M, at the London School of Hygiene and Tropical Medicine, Keppel Street, W C 1, Dr Gregory Pincus, research director of the Worcester Foundation for Experimental Biology, U S A, will give the Oliver Bird lecture He will speak on control of fertility with oral medication

The Royal Microscopical Society invites photomicrographic workers to submit entries to an exhibition which it is to hold at the Polytechnic, Regent Street, London, W 1 Further particulars may be had from R Setterington, hon secretary, Micro 58, Royal Microscopical Society, Tavistock House South, Tavistock Square, W C 1

The Hospitals' Symphony Orchestra is to give a concert at B M A House, Tavistock Square, London, W C 1, on Saturday, March 22, at 8 P M Tickets (7*s* 6*d*, 5*s*, and 3*s*) can be had from Patricia O'Hanlon, St Bartholomew's Hospital, E C 1

Doctors who wish to watch the Boat Race on April 5 from the Bemax premises should make early application to Dept B R I Vitamins Limited, Upper Mall, London, W 6

The address of the hon. secretary of the Rubella Children Parents Group is now Mrs Peggy Freeman, Rowland, 63, Horn Lane, Woodford Green, Essex The group was formed in 1955 to help parents with the education of children affected antenatally by rubella

Appointments

Adams, J C S, M B Edin, M R C P E assistant physician in geriatrics, Norfolk and Norwich area hospitals

Carslaw, J S, M B Glasg assistant M O H, Argyllshire

Hughes, J M, M B, B SC Wales, D P M assistant psychiatrist (S H M O), Whitchurch Hospital, near Cardiff

Lernihan, Mary G, M B N U I, D C H, D P H school M O and assistant M O H, Coventry

Lundholm, E O, M B Glasg, D P M psychiatrist (S H M O), East Lothian Mental Hospital, Haddington

Reinold, D G, M R C S surgical registrar, County Hospital, Doddington

Vaccaro, J G, M B Lond assistant M O, Buckinghamshire (Aylesbury area)

The Hospital for Sick Children, Great Ormond Street, London:

Clark, A C L, M D Melb, M R A C P house physician

Proby, Patience, M B Oxon, M R C P house-physician

Srinivasan, Hariharan, M B Madras, F R C S house-surgeon

Turner-Warwick, R T, D M, M CH, B SC Oxon, F R C S surgical outpatient assistant

Newcastle Regional Hospital Board

Lyon, W M M, M B Edin, M R C P E, D P M consultant psychiatrist and deputy medical superintendent, St Mary's Hospital, Stannington, near Morpeth

Rowbotham, Monica D, M B Manc, D P M assistant psychiatrist (S H M O) in child guidance, Newcastle group of hospitals

Sharp, C J, M B Leeds, D O assistant ophthalmologist (S H M O), Sunderland and Hartlepools groups of hospitals

Sykes, Peter, M B Sheff assistant psychiatrist (S H M O), Winterton Hospital, Sedgefield

Walton, J N, M D Durh, M R C P consultant neurologist, Regional Service and United Newcastle upon Tyne Hospitals

Woodford-Williams, Eluned, M D, B SC Lond, M R C P, D C H, D OBST senior consultant physician (geriatrics), Sunderland group of hospitals

Colonial Appointments

Conway, G F, M B Polish Sch of Med, Edin M O, Uganda

Davies, C W, M R C S, D P H D D M S, Uganda

Galt-Gamble, Margaret E, L R C P I, D P H senior M O, Ministry of Health, Ghana

Greenaway, D G G, M R C S M O, Uganda

Ground, K E A U, M R C S, D T M & H M O, Uganda

Lumsden W H R, M B, B SC Glasg, D T M & H director, East African trypanosomiasis research organisation, East Africa High Commission

McGregor J R, M B Edin., M R C P E specialist physician, Northern Region Nigeria

McHugh George, M B, B SC Glasg, D T M & H principal M O, Ministry of Health Ghana

Mackay, D H, M R C S, D P H, D T M & H medical superintendent, Nairobi Kenya

Mitchell, R M, M B Glasg, F R F P S M O (special grade), Tanganyika

Raffray, J R, M D Paris D D M S, Mauritius

The Lancet · Saturday 29 March 1958

"THESE DYING DISEASES" VENEREOLOGY IN DECLINE?*

AMBROSE KING
M B Lond , F.R C S
SENIOR PHYSICIAN,
THE WHITECHAPEL CLINIC, THE LONDON HOSPITAL, E 1

MY title is a quotation from the chairman of a regional hospital board, who, when approached about some very necessary reconstruction of a V D clinic, replied "We don't want to spend money on these dying diseases" It echoes an opinion which seems to be held by almost every doctor who is not in direct contact with the subject but is entirely contrary to the views and experience of most venereologists Workers in this field recall a similar episode twenty years ago When sulphonamides were introduced in 1937 it was commonly said that venereology would soon cease to exist as a special subject The years which followed were the busiest that most of us have ever spent

The Present Position

In this and other Western countries the incidence of the venereal diseases during the past twenty-five years has followed a well-recognised and expected trend—a steady decline during the 1930s, during times of peace and in association with more diligent methods of V D control, followed by a very great rise during the years of war, reaching a peak in 1946, a year after the war ended, and a steep decline during years of peace and plenty in which new and effective remedies became increasingly available Assuming that war or economic recession can be avoided, circumstances were never more favourable than they now are for complete control of these infections in a highly organised community such as our own, and the next few years should determine whether this degree of control is feasible

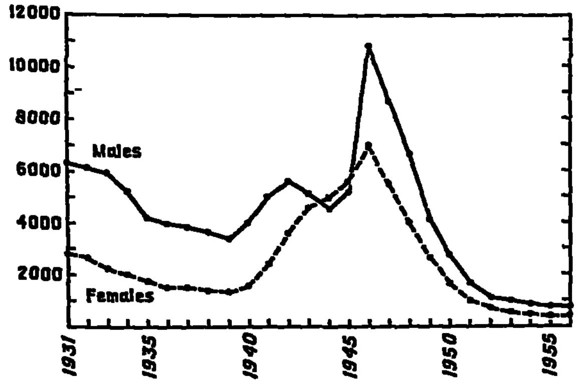

Fig 1—Number of cases of syphilis of less than a year s duration England and Wales.

SYPHILIS

Fig 1 shows the incidence of infectious syphilis—i e, cases of less than one year's duration—seen in V D centres of England and Wales from 1931 to 1956, as given in the annual reports of the Chief Medical Officer of the Ministry of Health The decline is spectacular, and the low level now reached is unprecedented In 1955 new cases were less than 5% of those in 1946—the year of highest post-war incidence Nevertheless it is noteworthy that in 1955, for the first time since 1947, the number of new patients attending with infectious syphilis failed to fall, the figures being 609 cases in the male and 228 in the female, as compared with 600 and 208 respectively in 1954 The corresponding figures for 1956 were 587 and 257 Thus, though at present there is no reliable evidence of a tendency to rise, it does seem that the progressive fall has come to an end These figures indicate trends rather than true incidence How many cases of venereal disease are treated outside the treatment centres is unknown, but probably few cases of early syphilis

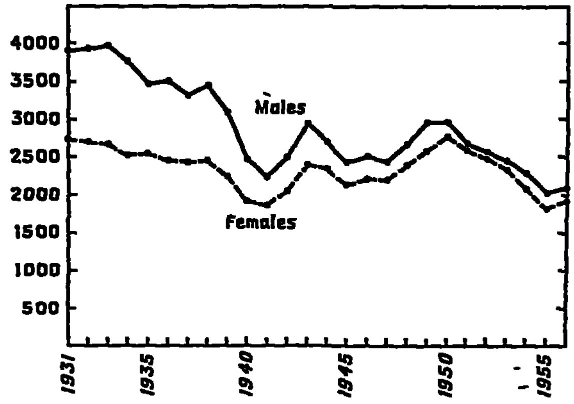

Fig 2—Number of cases of syphilis of more than a year s duration England and Wales

Experience suggests, however, that infectious syphilis often remains undiagnosed We might therefore expect a rise in the incidence of late syphilis following the high prevalence of early syphilis during and after the last war The reported figures do not bear this out (fig 2) Late and latent syphilis did not show an appreciable decline until 1952, but then fell consistently until 1955, rising slightly again in 1956 to the level of 2191 cases in men and 2106 cases in women The decline is greatest for cases of neurosyphilis, gummatous lesions, and late-latent syphilis, it is small for cardiovascular syphilis

It is hard to estimate the significance of these findings Much late syphilis is treated elsewhere than at the V D treatment centres, and this proportion may well have increased since treatment became safer and easier to

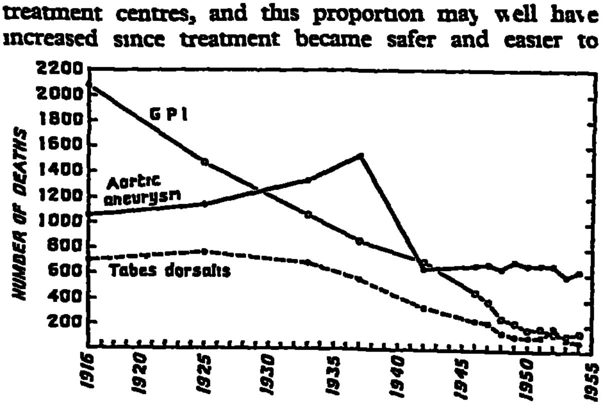

Fig 3—Mortality from late syphilis, England and Wales, 1916-54.

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* A shortened version of the Malcolm Morris memorial lecture given under the auspices of the Chadwick Trustees at St Mary's Hospital, London, on Dec 5, 1957

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administer The main antisyphilitic remedy is used freely for many other conditions Possibly this helps to prevent the late serious effects of syphilis, but it may suppress information which would help us to estimate the extent of the problem

Whatever the truth about the prevalence of late syphilis, there can be no doubt about the decline in mortality from the late manifestations Fig 3 shows the decline in mortality from general paralysis, tabes dorsalis, and aortic aneurysm from 1916 to 1954 Since 1954 there has been little change for general paralysis and a slight decline for tabes dorsalis On the other hand deaths from syphilitic aneurysm of the aorta have not declined to a similar extent for males and have risen for females It is clear that cardiovascular syphilis remains a serious problem It has become customary to give credit to penicillin for all the considerable advances made in the control of syphilis since the second world war, but there is no real evidence that penicillin, given for syphilis or for other infections, is the cause of the decline in mortality from late syphilis Fig 3 shows that during the ten years 1945–54, after penicillin became available, the rate of decline was less than in earlier years

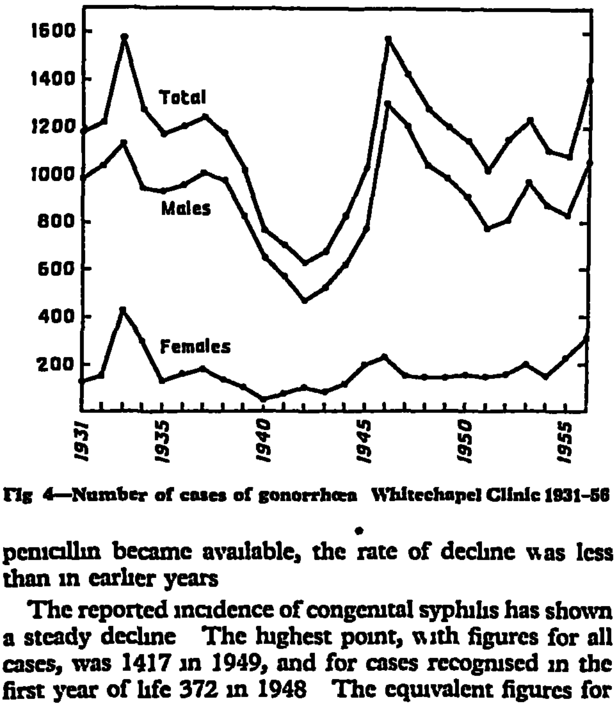

Fig 4—Number of cases of gonorrhœa Whitechapel Clinic 1931-56

The reported incidence of congenital syphilis has shown a steady decline The highest point, with figures for all cases, was 1417 in 1949, and for cases recognised in the first year of life 372 in 1948 The equivalent figures for 1956 were 590 and 36

It is interesting to study the position in the United States, where trends of incidence of venereal disease have been similar, bearing in mind that in that country penicillin has been even more generally used for the treatment of diseases other than syphilis and that routine serological tests for syphilis are more widely applied to the diagnosis of syphilis in its latent stages In February of last year a joint statement by the Association of State and Territorial Health Officers, the American Venereal Disease Association and the American Social Hygiene Association, drew attention to an increase in reported syphilis during 1956, for the first time since 1948 This increase was not large (4144 cases) but was general, including all forms of syphilis except early latent infection Yet, as Earle Moore (1957) pointed out, the progress made is substantial indeed (namely, a drop from a peak of 214,306 cases of actually or potentially infectious early syphilis in 1947 to 26,721 in 1956), but he believed that still further effort was necessary to maintain these gains and to provide a "standby nucleus" of venereal-disease control organisation in the event of a major increase from any cause

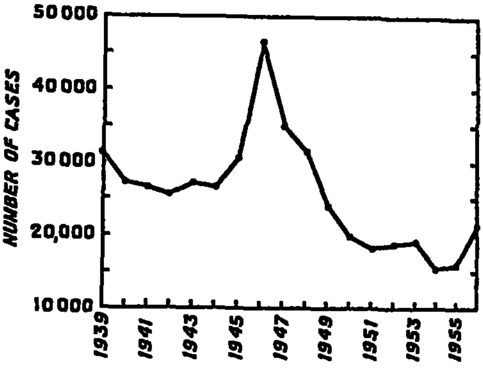

Fig 5—Gonorrhœa England and Wales 1939 56

We may say, therefore, that at present it is impossible to judge whether syphilis is yet under control in this or other Western countries

GONORRHŒA

In some respects gonorrhœa lends itself more readily to epidemiological study Its high prevalence, its short incubation period, the infrequency of undiagnosed infection (at any rate among men), and its variation with social and economic conditions, are all factors which facilitate study

Fig 4 shows the rise and fall in numbers of patients attending with acute gonorrhœa, during the last twenty-seven years, at the Whitechapel Clinic of the London Hospital which, in respect of the incidence of infection, may be regarded as representative of most clinics in large cities in this country Three peaks are seen the first coincides with the economic recession and mass unemployment of the early 1930s, the second reached its height in 1946, the year after the war, and the third was in 1956 This last is a point of particular interest The incidence for the country as a whole shows a similar peak for 1956 (fig 5) with an increase of about 10% over 1955 It seems, however, that the increase has so far been mainly limited to certain urban areas Fig 6 shows attendances of new patients with acute gonorrhœa at the Whitechapel Clinic month by month in 1955, 1956, and 1957 It will be seen that the increase noted in 1956 continued in 1957

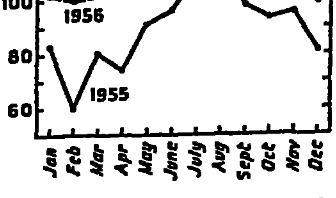

Fig 6—Gonorrhœa Whitechapel Clinic 1955–57

The figures for the United States show no similar rise, though the Joint Statement to which I have referred recorded that, since November, 1955, increases in gonorrhœa had been reported from sixteen States and twenty-two cities Comments from a number of States and cities suggest that the apparently favourable figures for some areas may be influenced by differences in reporting According to

Earl Moore (1957) no noteworthy progress has been made, or is in sight, in the control of gonorrhœa in the United States

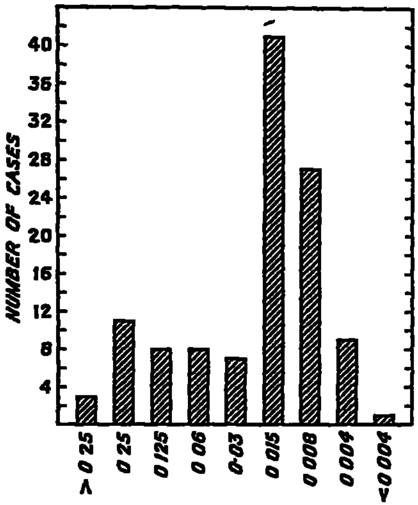

Fig 7—Gonococci from 115 cases

What are the factors responsible for the recent increase of gonorrhœa in this country ? Pronouncements about this must be largely speculative, but two factors are probably important

First there is evidence that penicillin-resistant strains of gonococci are now emerging Some cases of acute gonorrhœa fail to make any response to doses of penicillin which in the past were nearly always highly efficacious Repeated doses of penicillin and doubling the doses may have no effect In other cases, response seems satisfactory but relapse follows within a day or two Quantitative in-vitro tests for sensitivity to penicillin suggest that in these cases organisms from the secretions are considerably less sensitive to penicillin than the Oxford staphylococcus or other strains of gonococci The correlation between clinical findings and in-vitro tests is, as one might expect, close but not absolute Studies by F R. Curtis and A E Wilkinson at the London Hospital illustrate these points

Fig 7 shows the results of quantitative estimates of the penicillin sensitivity of gonococci from the secretions of 115 men with acute gonorrhœa Though most strains show high sensitivity, there is appreciable variation in the minimal inhibiting concentrations of penicillin

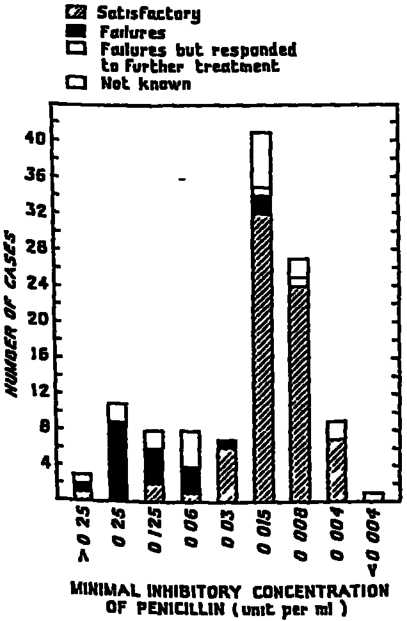

Fig 8—Gonorrhœa 95 cases Clinical outcome in relation to sensitivity to penicillin

Fig 8 relates these results to the clinical outcome in 95 cases in which the patients remained under observation The term " failure " indicates a complete absence of response to repeated doses of penicillin which in the past have nearly always proved adequate In some other cases there was no response at first, but further dosage of penicillin cleared the signs of infection It can be seen that, in general, the lower the sensitivity of the organism to penicillin in the test-tube, the greater the likelihood of clinical failure the higher the sensitivity the more probable the response to treatment (fig 9)

Most patients cease to attend after the discharge has ceased, so confident are they of the curative effect of the drug, but the spread of penicillin-resistant gonococci may mean that some cures are now more apparent than real, and that infectious latency is becoming more common Fortunately the penicillin-resistant strains of gonococci have so far appeared to be susceptible to streptomycin, but this is an antibiotic to which organisms readily become resistant, and it, too, may lose its effect.

The second factor which has probably affected the incidence of gonorrhœa in large cities is immigration from the West Indies and other parts of the Commonwealth

Hall (1957), himself a West Indian, speaking in 1956, estimated that there were 75,000 West Indians in Great Britain, distributed roughly as follows London, 30,000, Birmingham, 15,000, Manchester, 8000, Sheffield, 2500, Leeds, 3000, Liverpool, 12,000, and smaller numbers in Southampton, Coventry, and elsewhere It is perhaps significant that the greatest increase of gonorrhœa has been in London and Birmingham According to Hall, it has been established that the incidence of venereal disease in certain big cities in this country is closely related to the increasing population of West Indians He ascribed this fact to the following factors (1) The movement of population, with its attendant problems (2) The immigration is from a country in which the incidence of venereal disease is very high (3) Difficulties which the immigrants experience in relation to housing, which are made worse by colour prejudice (4) Difficulties related to recreational facilities and social contacts The number of West-Indian men is in no way balanced by the number of West Indian women Because of colour prejudice the West Indian men are extremely limited in their contacts with the opposite sex, so that the contacts they do make are with prostitutes leading to the spread of venereal disease

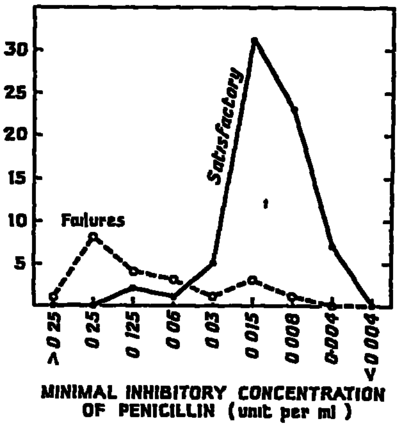

Fig 9—Gonorrhœa 95 cases Clinical outcome in relation to penicillin sensitivity

Table I shows the incidence by race of 925 cases of acute gonorrhœa seen at the Whitechapel Clinic during twelve months in 1955–56

During this period 3270 new male patients attended the clinic of whom 2193 were white and 1077 coloured

TABLE I—WHITECHAPEL CLINIC CASES OF GONORRHŒA BY RACE—NOVEMBER, 1955, TO NOVEMBER, 1956

Race	No	%
White (excluding Maltese)	402	43.5
Maltese	143	15.5
British West Indian	219	23.7
British West African	62	6.7
Indian	27	2.9
Pakistani	16	1.7
Other coloured	56	6.0
Total	925	100

The table shows that the incidence of gonorrhœa among coloured patients was out of proportion to their numbers

My own view, from seeing this problem in a limited area, is that the incidence of infectious venereal disease is not unduly high among these immigrants when they arrive in this country Upon arrival, they experience the stresses and strains of immigrants in strange surroundings, suffering from an uncongenial climate, restricted in social contacts, and sensitive to colour prejudices, some real and some imaginary In these circumstances, and because of the type of women with whom they associate, the spread of venereal disease is inevitable Some of these men suffer multiple infections, and, because of familiarity and a certain happy-go-lucky streak in their natures, may come to regard them very lightly

The importance of prostitutes in spreading gonorrhœal infection should not be underestimated

In a study by the British Cooperative Clinical Group (1956) information was collected from representative clinics throughout the country relating to 7157 patients suffering from gonorrhœa of whom 6004 were men and 1153 women No less than 215 (18 6%) of the infected women admitted that they were prostitutes, and of 5328 men who gave information about the source of infection 1893 (35 5%) said that their infection had been acquired from prostitutes Laird (1956) gave details from two large clinics for venereal disease in Manchester, which showed that in the year ended June 30, 1956, 876 (26%) of 3325 men attending for advice had consorted with prostitutes During this period 30% of gonococcal infections and 25% of "non-specific" genital infections were acquired from prostitutes Keighley (1957) examined and tested 169 prostitutes admitted to Holloway Prison during 1956 32% of them had gonorrhœa

It seems, therefore, that prostitutes, and particularly seaport prostitutes who are perhaps repeatedly infected by overseas contacts, are one of the principal agents in maintaining the spread of infection

CHANCROID

Chancroid has never been common in this country and is mostly limited to seaports In England and Wales the reported cases for 1956 were 316, compared with 1028 in 1946—the year of highest incidence during and after the last war

NON-SPECIFIC GENITAL INFECTION

Non-specific infection, sometimes known as abacterial urethritis, or (in its complicated form) as Reiter's disease, is now the major problem in V D clinics In incidence it is second only to gonorrhœa, and it often proves intractable The clinical appearances are fairly easily distinguishable in the male but are not characteristic in the female Thus, in the absence of a known specific cause, diagnosis in the female is usually based on known infection of contacts

The figures from the Chief Medical Officer's reports, covering the years since 1951 when these infections were first included in the annual returns from clinics, show only numbers of infections in men (fig 10) In the male, 13,157 cases of non-gonococcal urethritis were treated in 1953, compared with 15,242 cases of gonorrhœa This figure of 13,157 was appreciably higher than the 1952 figure of 11,552 cases By 1956 the number was 14,825

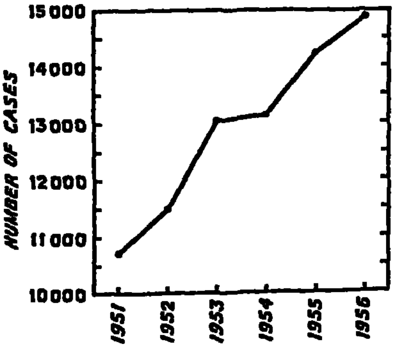

Fig 10—Non-specific genital infection Men England and Wales 1951-56

It is becoming apparent that this infection is the cause not only of acute attacks of arthritis but also of chronic relapsing and sometimes progressive arthritis which may lead to severe and crippling deformities, in association with chronic prostatitis, which is a common and intractable effect of the disease The arthritic manifestations may follow years after the infection has been assumed to be cured, in fact, the symptoms of initial genital infection may be so slight that the patient may remain unaware of it and the correct diagnosis may be missed This is probably a major cause of rheumatism and arthritis, which may prove very resistant indeed to treatment

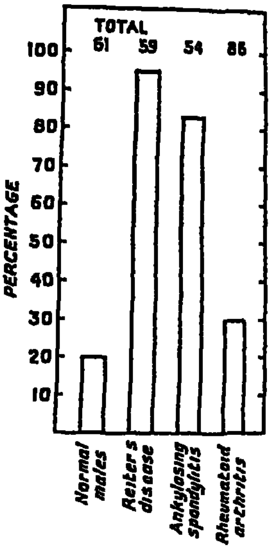

Fig 11—Incidence of chronic prostatitis

Increasing attention is also focusing upon this infection as a possible cause of ankylosing spondylitis and relapsing iritis J K Oates at the London Hospital recently investigated the incidence of chronic prostatitis in a series of cases of Reiter's disease, of ankylosing spondylitis, and of rheumatoid arthritis, with presumed normals to act as controls (The term Reiter's disease is used here for the association of genital infection with arthritis and other metastatic effects It does not necessarily mean the triple syndrome of urethritis, arthritis, and conjunctivitis) Fig 11 shows that 95% of 59 patients with Reiter's disease and 83% of 54 with ankylosing spondylitis had chronic prostatitis In contrast, evidence of chronic prostatitis was found in 30% of 86 men with rheumatoid arthritis and 20% of 61 men presumed to be normal

Little is really known about the relation between so-called non-specific genital infection and these serious conditions The subject is of immense importance and merits intensive investigation which might shed entirely new light on the causation of rheumatic diseases

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum has always been regarded as uncommon here, and returns from the V D treatment centres have been scanty Nevertheless the Chief Medical Officer's report for 1955 records an appreciable increase of this disease in that year (from 63 cases in 1954 to 86 in 1955) The figure for 1956 was 83 A recent investigation (King, Barwell, and Catterall 1956) suggested, however, that the incidence was higher than had been suspected, and that cases were perhaps being missed During the period November, 1954, to December, 1955, 1317 patients attending the Whitechapel Clinic for the first time had routine intradermal tests with a yolk-sac antigen of the virus of lymphogranuloma venereum (Frei test) Assessment of the results was possible in 1119 cases (table II)

TABLE II—RESULTS OF ROUTINE INTRADERMAL (FREI) TESTS

Routine intradermal test -	Men	Women	Total
Total number tested	1092	225	1317
Excluded through default	176	22	198
Total under consideration	916	203	1119
Positive tests	178	28	206
Percentage positive tests	19 4	13 8	18 4

The intradermal tests were positive in 206 cases (18 4%)

TABLE III—RESULTS OF COMPLEMENT-FIXATION TESTS FOR LYMPHOGRANULOMA VENEREUM

—	Men	Women	Total
Positive intradermal test	178	28	206
C F T positive at 1 in 32 or above	18	5	23
C F T positive in lesser dilution	136	21	157
C F T negative	24	2	26
Percentage of Frei-positive patients with proven lymphogranuloma venereum	10	18	11
Percentage of total patients tested with proven lymphogranuloma venereum	1 9	2 5	2

In 23 of these cases (2% of the total) the diagnosis of lymphogranuloma venereum was confirmed by strongly positive complement-fixation tests (table III) A considerably larger number of patients (157) showed complement-fixing antibodies in the blood-serum, but not—by the strict standards employed—in sufficient quantity to justify a firm diagnosis of active infection Of the 23 patients found to have lymphogranuloma venereum, only 1 had clinical evidence of the infection which was detected before the intradermal test In 9 other cases re-examination showed clinical evidence which had been missed

The incidence of positive intradermal tests and also of proven lymphogranuloma venereum was relatively higher in the smaller number of Negroes examined (table IV), but there was nothing to suggest that the recent influx of coloured population from the West Indies has had much effect on the incidence of this disease in the white population

TABLE IV—COMPARISON OF WHITES AND NEGROES INTRADERMAL TEST AND COMPLEMENT-FIXATION TEST

Race	Sex	No tested	Intradermal test positive		C F T			
					+		±	–
			No	%	No	%		
Whites	Men	813	132	16	12	1 5	102	18
	Women	178	19	11	2	1	16	1
Negroes	Men	93	46	50	6	6	34	6
	Women	25	9	36	3	12	5	1

Thus these findings suggested that there is an appreciable amount of undiagnosed lymphogranuloma venereum in the population of the East End of London Whether other areas are similarly affected only further investigation can determine

GRANULOMA INGUINALE

Granuloma inguinale has always been regarded as a rarity in this country, limited to occasional cases at seaports The first period for which records are available was 1951, when 2 cases were reported in England and Wales During 1952, 6 cases were reported, in 1953, 2 cases, in 1954, 9 cases, in 1955, 9 cases; and in 1956, 15 cases Knight and Fowler (1956) reported 8 cases from the Birmingham area recognised between July, 1955, and October, 1956 In our own clinic we have had 2 cases of this condition within the last few weeks In each case the diagnosis was not suspected on clinical grounds but was reached as the result of microscopic section after biopsy

Presumably the increase of this still rare disease results from immigration from countries where it is endemic The fact that it is beginning to appear and may be difficult to diagnose is worth noting, even though it is not of great importance at present

Work of the Treatment Centres

Thus, judging by attendances at the treatment centres, since the war there has been a notable reduction in infectious syphilis (of less than a year's duration) and congenital syphilis, with a less striking reduction in cases of late syphilis Gonorrhœa, after a steep fall for some years, is now considerably more prevalent Chancroid has declined from an incidence which was never high Non-specific genital infection is now recognised as a major and growing problem Lymphogranuloma venereum is seldom diagnosed but there is reason to suppose that it is not rare Cases of granuloma inguinale are beginning to appear in small numbers

It should be noted that the decline in the incidence of some veneral diseases has not been accompanied by a similar fall in the *total numbers of new cases* attending the treatment centres (table V)

TABLE V—TOTAL NEW CASES ATTENDING THE V D CLINICS OF ENGLAND AND WALES

1925	71,431	1936	85,737	1947	140,686
1926	74,644	1937	89,375	1948	132,065
1927	81,853	1938	90,678	1949	116,075
1928	85,908	1939	83,224	1950	110,829
1929	86,521	1940	72,052	1951	97,231
1930	90,984	1941	77,229	1952	97,154
1931	87,421	1942	84,928	1953	98,593
1932	86,554	1943	117,362	1954	93,747
1933	87,508	1944	116,538	1955	94,698
1934	89,636	1945	133,777	1956	98,212
1935	86,656	1946	177,963		

From 1925 to 1942, the number fluctuated between 70,000 and 91,000, and then rose sharply to nearly 178,000 by 1946 Apart from the eight years 1943–50, the figure of 98,593 for 1953 was actually the highest since the figures were first published in 1925 These trends are illustrated in fig 12

A memorandum entitled Venereology and the Future, prepared in 1955 by the council of the Medical Society for the Study of Venereal Diseases, pointed out that one reason for the disparity between the number of new cases of infectious venereal disease and the total attendances of new cases at the V D treatment centres is the fact that the official definition of venereal disease is limited to three conditions—syphilis, gonorrhœa, and soft chancre All other diseases are classified as " other conditions ", which include non-gonococcal urethritis and its complications, trichomoniasis, lymphogranuloma venereum, granuloma inguinale, and a variety of other conditions affecting the genitalia

It should be noted, too, that no less than 32,349 new

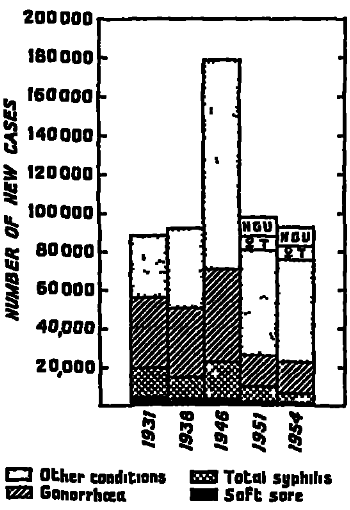

Fig 12—New cases Diagnoses England and Wales 1931–54

N G U.—non-gonococcal urethritis in the male

♀T—non-gonococcal discharges in the female patients (23,514 men and 8835 women) attended the treatment centres for advice during 1956 and required no treatment The fact that so many anxious people seek advice for problems of this kind is evidence of the confidence which the public places in these institutions, and their usefulness in preventing psychogenic illness should not be overlooked

Apart from new patients, it is true that attendances of patients to see the doctors has fallen considerably The figures for 1934 were 1,547,062, for 1944, 1,388,258, for 1954, 756,922, and for 1956, 685,819 This is the result of better methods of treatment and is a most welcome development It has made possible a general rise in the standards of work with fuller examination of the patient and more collateral attention

In the diagnosis of syphilis new problems have arisen As the disease has continued to decline, and penicillin has been used for a wide variety of non-syphilitic conditions, it has become more difficult to tap the reservoirs of hidden infection For this reason the Chief Medical Officer's report for 1952 recommended routine serological testing of hospital inpatients and outpatients, of candidates for insurance, and of personnel demobilised from the Services The memorandum to which I have referred laid stress on the continued importance of routine serological testing of expectant mothers, blood donors, and other groups, so that the late cases of syphilis resulting from undiagnosed disease acquired during or after the second world war could be detected while the disease was still latent There was a good case for routine serological tests of all patients admitted to general and mental hospitals—a practice which has never been generally adopted in this country Those who were most likely to have acquired the disease unwittingly were now older, and it seemed reasonable to pay particular attention to routine serological testing of the elderly

Furthermore, as the incidence of syphilis declined, the problem of biological false-positive results to standard serological tests became proportionately more important In recent years new and more specific serological tests for syphilis have been evolved, which depended on antibodies other than the " reagin " detected by standard serological tests The most reliable, and the most complex, of these is the treponemal immobilisation test Other more simple agglutination and complement-fixation tests are being explored, but their value is as yet unproven

The Present Position of Venereology

I hope that the picture I have drawn will suffice to show that the venereal diseases, despite persistent rumours to the contrary, are not dead or even dying Even in present favourable circumstances they are a considerable problem, and in the event of war or economic depression they may again become epidemic Modern developments have in some respects complicated their management

Venereology is by no means limited to techniques of treatment, but is an important branch of general medicine closely related to the work of the general physician At the same time it is a vital part of preventive medicine, and it is mainly in this respect that physicians, dermatologists, urologists, and others who have practised it in the past have often failed to measure up to proper standards In this country the V D service has been organised over the years with efficiency, economy, and considerable success It has deserved well of the public, and the public has shown its confidence by increasing willingness to use it

In a review of the specialist medical services by the Ministry of Health in 1955, it appeared that the V D service is maintained by only 93 consultants and 79 senior hospital medical officers The proportion of consultants to S H M O s is considerably lower than that of the specialist services as a whole (fig 13) Apparently, too, venereologists are generally older than consultants in the specialised services as a whole, and, assuming retirement at 65 years, retirement will in general be more rapid in venereology Despite this apparently favourable sign there were in 1955 only 9 senior registrars in training as venereologists

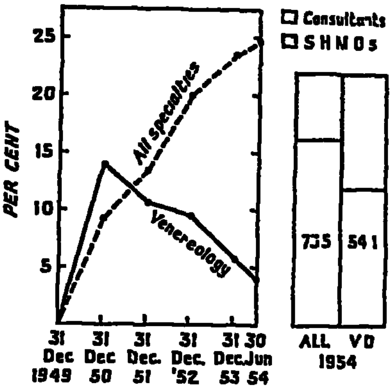

Fig 13—Specialist services Consultants and senior hospital medical officers

The memorandum of the council of the Medical Society for the Study of Venereal Diseases considered the factors likely to be responsible for the lack of attraction of this specialty to young doctors High on the list were the misguided but frequent suggestions that the venereal diseases are finished and that the subject holds no prospects for newcomers To add point to these fears was the fact that since 1950 the specialised services in general had expanded but the number of consultants in venereology had diminished, owing to the closing of certain clinics and failure to fill other vacancies (fig 13) In other instances vacant posts had been filled by persons who, however well trained in other respects at the time of assuming office, had not completed what the council regarded as sufficient training in venereology This was very discouraging to the small group of senior registrars in venereology who had some reason to expect that their years of training would be rewarded, and their discouragement was in turn transmitted to others who might have followed the specialty In addition, venereology had always been to some extent inherently unattractive because V D clinics often operate at late and awkward hours, in departments which may be structurally isolated from other parts of the hospitals Students and others attending the clinics at specified times have not always enjoyed the same close association with the consultants as they do in other medical and surgical work Hence they have had less opportunities for learning of the attractions of the subject

Plans for the Future

It seems, then, that although the venereal diseases are certainly not dying, there is a danger of the decline of venereology The combination of thriving diseases and the disappearance of those whose special study they are has obvious dangers for the public health

It seems essential that the structure of the V D service should be maintained The first step is to correct those who have falsely interpreted a post-war decline and a new remedy as the end of a major problem Where work has to be done in the diagnosis and treatment of venereal diseases, a venereologist should be appointed, and nowhere is this more important than at teaching hospitals

Vacancies in this special subject should always be advertised and should be filled by properly trained venereologists —not by dermatologists, genitourinary specialists, or others without training of the appropriate kind It should be realised, too, that there are many big gaps in our knowledge, and that fundamental research is a paramount need for the purpose of progress as well as for the encouragement of young men entering the specialty

In the campaign against these tough and enduring enemies of the human race, we must look beyond the dust of a single battle If we disband our forces after a single victory the war will certainly be lost and the casualties may be very heavy indeed

Summary

The reduction in venereal diseases since the second world war probably owes more to favourable social conditions than to new remedies In respect of only one disease, syphilis, is there evidence of considerable success in the campaign for control, and even for syphilis the ultimate outcome remains in doubt. Gonorrhœa threatens again to become very serious, and solution of the major problem of non-specific genital infection is not in sight There are reasons for thinking that the incidence of lymphogranuloma venereum and even of granuloma inguinale may be increasing

The post-war decline in incidence, and the introduction of new remedies, have inspired a false confidence and a move to dismantle some of the organisation which has served the public well in the control of these diseases Because of this attitude it has been difficult to recruit young men of quality to this special subject. There is a case for strengthening rather than weakening the venereal-diseases scheme and for offering encouragement to new entrants by filling vacant appointments with venereologists and by financing research

I am grateful to Dr G L M McElligott, Dr R. R Willcox, and Prof E Gurney Clark, of Columbia University, New York, for help with facts and figures

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"I have never known anyone who impressed me as a real person whose world did not seem very real indeed to him It may be a three-ring circus, or it may be another Golgotha—or anywhere between But, in any case, it is a real place, with issues and actions that matter In the effort to take the world as a real place and not evade its reality, you may on occasion find wisdom in the art of taming, in taking advantage of the fact that life ebbs and flows, that the work of the world, like the work of the heart, goes on by means of diastole as well as systole, that children pass through phases, that enough is enough, that a sense of humor and proportion has its uses as well as being perfectly delightful, and that 'good horse sense' is the sense that horses have, never to bet on human beings'"
—ALAN GREGG, M D *For Future Doctors* Chicago and London, 1958

EFFECT OF SMOKING ON THE PRODUCTION AND MAINTENANCE OF GASTRIC AND DUODENAL ULCERS

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THE belief that peptic ulcers are aggravated by smoking has been held widely for many years Medical opinion has, however, not been unanimous and the published data, reviewed by Batterman and Ehrenfeld (1949), are inconclusive In their experience these workers found that medical treatment was more effective, and that recurrence of symptoms was less common, in patients who stopped smoking than in patients who continued to smoke On the other hand, Jamieson et al (1946) found that changes in the amount of tobacco smoked after treatment for a perforated peptic ulcer were unrelated to the severity of the subsequent symptoms

Observations on the effect of smoking on the secretion and motility of the stomach have also given varied results in both ulcer patients and healthy persons The experimental conditions have, however, varied, and it is difficult to draw any definite conclusions from these observations, except that the stomach is sensitive to one or more substances in tobacco smoke, and that different people may react to them differently (Batterman 1955)

In these circumstances, it was thought necessary to obtain further data A comparison was therefore made of the smoking habits of patients with and without peptic ulcer, and the effect of advising patients to stop smoking was tested by a controlled clinical trial

Smoking Habits of Patients with and without Peptic Ulcers

Patients Studied

For the analysis of smoking habits advantage was taken of the fact that a large amount of data had been collected by Prof Bradford Hill and one of us (R D) in the course of another investigation (Doll and Hill 1950, 1952) The patients whose smoking habits had been recorded had many different diseases and included some who had been admitted to hospital for treatment of a peptic ulcer The number of ulcer patients was, however, small, so that additional patients known to have a peptic ulcer were interviewed in the gastroenterological department of the Central Middlesex Hospital in 1950–51 (during the latter half of the earlier study) In both series the smoking histories were obtained by the same full-time research assistants, and the data were recorded on similar standard questionnaires

For the present purpose data were excluded in the following circumstances

(i) If the patients had been diagnosed as having "dyspepsia" or "gastritis,' because a proportion of these patients may well have had an unrecognised peptic ulcer

(ii) If the patients had been diagnosed as having a disease known or suspected to be associated with smoking (cancer of the lung or of the upper respiratory or upper digestive tracts, coronary thrombosis, angina pectoris, thromboangiitis obliterans, chronic bronchitis, or pulmonary tuberculosis)

(iii) If the patients were known to have had both gastric and duodenal ulcers, or were diagnosed as having a peptic ulcer of uncertain site These last were excluded because it was thought

TABLE I—MOST RECENT AMOUNT OF TOBACCO SMOKED REGULARLY BEFORE ONSET OF PRESENT ILLNESS IN GASTRIC-ULCER AND DUODENAL-ULCER PATIENTS AND MATCHED CONTROL PATIENTS

Disease group	No of non smokers	No smoking daily			
		1 g –	5 g –	15 g –	25 g +
Men					
235 gastric-ulcer patients	3 (*1 3%*)	8 (*3·4%*)	125 (*53 2%*)	74 (*31 5%*)	25 (*10 6%*)
470 controls	22 (*4 7%*)	37 (*7 9%*)	225 (*47 9%*)	133 (*28 3%*)	53 (*11 3%*)
284 duodenal ulcer patients	6 (*2 1%*)	13 (*4 6%*)	155 (*54 6%*)	81 (*28 5%*)	29 (*10·2%*)
568 controls	33 (*5 8%*)	26 (*4 6%*)	280 (*49 3%*)	157 (*27 6%*)	72 (*12 7%*)
Women					
92 gastric-ulcer patients	47 (*51 1%*)	10 (*10 9%*)	30 (*32 6%*)	4 (*4 3%*)	1 (*1 1%*)
184 controls	123 (*66 8%*)	25 (*13 6%*)	26 (*14 1%*)	8 (*4 3%*)	2 (*1 1%*)
54 duodenal-ulcer patients	29 (*53 7%*)	5 (*9 3%*)	16 (*29·6%*)	3 (*5 6%*)	1 (*1 9%*)
108 controls	67 (*62 0%*)	11 (*10 2%*)	20 (*18 5%*)	8 (*7·4%*)	2 (*1 9%*)

Difference between proportions of non smokers and smokers in study group and in corresponding control group

Men with gastric ulcers $\chi^2 = 5\ 31$, n = 1, P = 0 02

Women with gastric ulcers $\chi^2 = 6\ 44$, n = 1, P = 0 01

Men with duodenal ulcers $\chi^2 = 5\ 93$, n = 1, P = 0 02

Women with duodenal ulcers $\chi^2 = 1·04$, n = 1, P > 0 1

better to compare the smoking habits of patients with gastric ulcers and of patients with duodenal ulcers separately

The remaining patients were divided into two study groups (patients with gastric ulcers and patients with duodenal ulcers) and a third group consisting of patients with all other diseases

The smoking habits of these groups cannot be compared with one another directly, because the groups differed with respect to several factors known to be related to smoking Such factors include sex, age, social status, and place of residence Control groups were therefore chosen from among the patients with non-ulcer diseases, such that each ulcer patient was matched by two control patients of the same sex, the same five-year age-group, and the same type of place of residence, male patients were also matched for the same socio-economic class For this purpose patients were divided into four residential groups (Greater London, county boroughs outside Greater London, other urban districts, and rural districts), and the male patients were divided into three socio-economic classes—the Registrar General's classes 1 and 2, class 3, and classes 4 and 5 (Registrar General 1951)

When more than two suitable patients were available to match each ulcer patient, the choice of the control patient was made by reference to a series of random numbers When, as happened occasionally in the younger age-groups, there were insufficient control patients, the number of ulcer patients was reduced in the same way Finally, there were available for analysis data relating to 327 patients with gastric ulcers, 338 patients with duodenal ulcers, and 1143 control patients with diseases believed to be unrelated to smoking The total number of control patients was less than double the number of ulcer patients because 187 were matched with patients in both ulcer groups

Results

Comparisons of the smoking habits of the gastric and duodenal ulcer patients with the habits of the corresponding groups of "matched controls" are shown in tables I–III Table I shows the numbers of non-smokers in each group and the number of patients who were smoking different quantities of tobacco before the onset of the illness which brought them to hospital If the patients had previously given up smoking, they were classified according to the quantities smoked immediately before they last gave up For the purpose of this analysis a non-smoker is defined as a person who has never consistently smoked as much as 1 g of tobacco a day—i e, one manufactured cigarette a day or $^1/_4$ oz of tobacco a week—for a year If the illness which brought the patient to hospital was remittent, the onset of the illness was regarded as the onset of the bout (or series of bouts) which, in the patient's opinion, brought him to hospital

The results show that, for both sexes, the proportions of non-smokers were smaller in the ulcer groups than in the corresponding control groups gastric ulcer, men 1 3% against 4 7%, women 51 1% against 66 8%, duodenal ulcer, men 2 1% against 5 8%, women 53 7% against 62 0% In the case of gastric ulcer the differences were statistically significant for both sexes, but in the case of duodenal ulcer they were significant only for men The gastric ulcer patients also included a smaller proportion of very light smokers (smokers of 1–4 g a day) than their controls, but, in this respect, there was practically no difference between the duodenal ulcer patients and their controls The proportions of smokers in the two heaviest smoking categories showed no corresponding differences between the disease groups, and the excess of smokers among the ulcer patients was concentrated almost entirely in the middle group of patients smoking 5–15 g a day There was therefore no progressive and consistent change in the relative proportions of patients in the study and control groups as the amount smoked increased

The age at which smoking was begun is shown in table II The male patients with gastric ulcers started smoking somewhat earlier in life than their controls,

TABLE II—AGE AT STARTING TO SMOKE GASTRIC-ULCER AND DUODENAL-ULCER PATIENTS AND CONTROLS

Disease group	No and age at starting		
	Men under 15 yr Women under 20 yr	Men 15–19 yr Women 20–29 yr	Men 20 yr or more Women 30 yr or more
Men who smoked			
232 gastric-ulcer patients	46 (*19 8%*)	145 (*62 5%*)	41 (*17 7%*)
448 controls	63 (*14 1%*)	278 (*62 1%*)	107 (*23 9%*)
278 duodenal-ulcer patients	40 (*14 4%*)	188 (*67 6%*)	50 (*18 0%*)
535 controls	100 (*18 7%*)	322 (*60 2%*)	113 (*21 1%*)
Women who smoked			
45 gastric ulcer patients	7 (*15 6%*)	10 (*22 2%*)	28 (*62 2%*)
61 controls	12 (*19 7%*)	23 (*37 7%*)	26 (*42·6%*)
25 duodenal ulcer patients	7 (*28 0%*)	11 (*44 0%*)	7 (*28 0%*)
41 controls	14 (*34 1%*)	10 (*24 4%*)	17 (*41 5%*)

Difference between proportions starting at different ages in study group and in controls

Men with gastric ulcers $\chi^2 = 5·93$ n = 2 P = 0·05

Men with duodenal ulcers χ^2 = [illegible]·47, n = 2, P > 0 1

Women with gastric ulcers $\chi^2 = 4\ 19$ n = 2, P > 0 1

Women with duodenal ulcers $\chi^2 = 2\ 84$, n = 2, P > 0 1

TABLE III—METHOD OF SMOKING BY MEN BEFORE ONSET OF PRESENT ILLNESS GASTRIC-ULCER AND DUODENAL-ULCER PATIENTS AND CONTROLS

Disease group	No smoking		
	Cigarettes only	Cigarettes and pipes	Pipes only
232 gastric ulcer patients	212 (*91 4%*)	9 (*3 9%*)	11 (*4 7%*)
448 control patients	354 (*79 0%*)	46 (*10 3%*)	48 (*10 7%*)
278 duodenal ulcer patients	237 (*85 3%*)	27 (*9 7%*)	14 (*5 0%*)
535 control patients	433 (*80 9%*)	50 (*9 3%*)	52 (*9 7%*)

Difference between proportions smoking by different methods in study group and in control group

Men with gastric ulcers $\chi^2 = 16\ 80$, n = 2, P < 0 001

Men with duodenal ulcers $\chi^2 = 5\ 38$, n = 2, P = 0 07 but no such tendency is evident for the female patients In neither sex was there any significant difference between the age at which the duodenal patients and the corresponding controls began

The method by which the tobacco was smoked is shown in table III Higher proportions of the male ulcer patients than of the corresponding controls smoked cigarettes The excess was most obvious for the gastric ulcer patients (91 4% against 79 0% for the controls), in this case there were deficiencies of both mixed smokers of pipes and cigarettes and of pipe smokers alone, and the differences were highly significant ($P<0\ 001$)

Trial of Effect of Stopping Smoking on Rate of Healing of Gastric Ulcers

The trial was conducted as part of a long-term investigation into the factors affecting the rate of healing of gastric ulcers The type of patients admitted for treatment and the general plan of the investigation have been described in detail in previous papers (Doll and Pygott 1952, 1954)

In brief, patients with gastric ulcers diagnosed radiographically for the first time were admitted to hospital and treated in a standard way for a week, during this time their clinical condition was assessed, and the barium examination was repeated Patients in whom the ulcer niche was less than 10 sq mm in area in profile and patients for whom surgery was considered desirable were excluded from the trial, the remaining patients were treated in bed in hospital, and a further barium-meal examination was made twenty-eight days after the previous examination. The results of treatment were assessed objectively by measuring the reduction in the size of the ulcer niche and subjectively by the patient's description of his symptoms In the present trial the results were also assessed by the change in the patient's weight

As in previous trials, two or three treatments were tested concurrently The individual treatments were, however, allocated in such a way that the group of patients given any one treatment and the group of patients not given it contained equal numbers of patients given each of the other treatments This was ensured by allocating the various combinations of treatments in equal proportions but in random order by opening a series of sealed envelopes which had been prepared previously The value of each method of treatment could then be assessed independently by comparing the results in those who had been given the treatment with the results in those who had not

Since, in the present trial, it was desired to test the effect of stopping smoking, patients were initially divided into two groups—smoking and not smoking For this purpose a patient was regarded as smoking if (1) he had at any time regularly smoked as much as one cigarette or 1 g of pipe tobacco a day for as long as a year, and (2) he had continued to smoke during the week before admission All others were regarded as not smoking

The effect of advising patients to stop smoking could be assessed only on those in the smoking group, half of them were therefore advised to stop, and half were not given any advice about their smoking habits and were allowed to smoke as much as they wanted The non-smoking patients were treated separately, and all were advised to continue to abstain from smoking Altogether 104 patients were included in the trial—80 smoking and 24 not smoking

The additional contrasting treatments given varied in the course of the trial For the first 64 patients (48 smoking and 16 not smoking) they were (1) continuous intragastric milk drip or no drip, and (2) a standard ulcer diet or an "almost normal" ward diet For the last 32 patients (24 smoking and 8 not smoking) they were an "almost normal" ward diet modified to contain either a high content of fat (150 grammes) or a low content of fat (50 grammes) The 8 intermediate patients (all smoking) received the "almost normal" diet with a daily addition of $^1/_2$ lb of calf's brain The effects of these treatments have been, or will be, reported separately (Doll, Price, Pygott, and Sanderson 1956, Doll, Friedlander, and Pygott 1956, Doll and Pygott 1958)

TABLE IV—COMPARABILITY OF PATIENTS ON ADMISSION AS REGARDS PAIN, BODY-WEIGHT, AND SIZE OF ULCER

Clinical and radiographic features	No of patients	
	Advised to stop smoking	Not advised to stop smoking
Pain on admission		
Present	26	25
Absent	14	15
Weight on admission		
Less than 8 st.	6	8
8 st.—	10	16
9 st.—	7	7
10 st.—	10	4
11 st.+	6	4
Not recorded	1	1
Initial size of ulcer niche		
10–24 sq mm	6	10
25–49 ,,	10	8
50–99 ,,	10	5
100+ ,,	14	17

Initial Comparability of Patients

In the absence of certain knowledge of the clinical features which affect prognosis the only precautions taken to make the patients given the different treatment comparable before treatment was started were the exclusion from the trial of patients who had been treated previously and had relapsed, and the allocation of the methods of treatment at random The comparability of the patients with regard to those features which are directly relevant to the method by which the results were assessed is shown in table IV which shows that the proportions of patients who complained of pain on admission were similar, but that rather fewer of the patients who were advised not to smoke had very small or very large ulcers, and substantially fewer of them weighed less than 9 stone. These two differences are therefore taken into account in the assessment of the results

Results

The change in size of the ulcer niche during treatment is shown in table V The niche diminished in size by two-thirds or more among rather more of the patients who were advised to stop smoking than among the patients who were not advised to stop smoking (30/40 against 23/40), and a somewhat bigger difference was found between the two groups in the average reduction in size of the ulcer niche (78 1% against 56 6%) This latter difference cannot be attributed to the difference in the proportion of ulcers of different initial sizes, because the treated group included a greater proportion of patients with moderate-sized ulcers (25–99 sq mm), and the average amount of healing in this group was slightly less than that for ulcers of more extreme sizes (66 6% healing against 67 9%) Possibly the difference is a chance finding unrelated to the methods of treatment, but this is not

TABLE V—EFFECT OF TREATMENT ON THE SIZE OF ULCER NICHE

Treatment group	No of patients	No of patients with ulcer niche					Average reduction (% of initial size of ulcer niche)
		Healed	67–90% smaller	34–66% smaller	0–33% smaller	Larger	
Patients advised to stop smoking who stopped completely	22	7	12	3	0	0	83 2
Patients advised to stop smoking who did not stop	18	4	7	5	2	0	71 8
All patients advised to stop smoking	40	11	19	8	2	0	78 1
Patients not advised to stop smoking	40	10	13	7	6	4	56 6
Total	80	21	32	15	8	4	67 4

very likely This can be shown by pairing the patients in the two groups according to the types of ancillary treatment used and the date of admission to the series, the significance of the mean difference between the reduction in size of the ulcer in each pair of patients can then be tested by the "t" test (mean difference 21 5%, t = 2 25, n = 39, P = 0 03) It may be noted, moreover, that the proportion of ulcers in the treatment group which were healed by two-thirds or more (75%) and the average reduction in the size of the ulcer (78 1%) are the best results yet to have been obtained with any of the special treatments investigated in a long series of clinical trials

Further evidence that the improvement is, in fact, due to the treatment is provided by the difference in the response of those patients who followed the advice and those who did not Table v shows that the average reduction in the size of the ulcer among those patients who did not stop smoking but who, for the most part, reduced their tobacco consumption substantially was intermediate between that for those who stopped completely and that for those who were not advised to modify their smoking habits at all 71 8%, 83 2%, and 56 6% *

In view of these findings the results obtained in patients who were not smoking on admission are somewhat unexpected Of 24 such patients the ulcer healed by two-thirds or more in 14 (58%), and the average reduction in size of the ulcer was 61 3% The results are almost identical with those obtained in the control series of patients who were smoking and were not advised to modify their habits (healed by two-thirds or more 58%, average reduction in size 56 6%)

TABLE VI—EFFECT OF TREATMENT ON BODY-WEIGHT

Initial body-weight	Treatment	No of patients	Average gain in weight (lb)	Standard deviation (lb)
Less than 9 st	Advised to stop smoking	16	8 8	3 1
	Not advised to stop smoking	24	6 9	3 0
9 st or more	Advised to stop smoking	23	6 5	3 6
	Not advised to stop smoking	15	5 2	3 6
All weights	Advised to stop smoking	39*	7 5	3 5
	Not advised to stop smoking	39*	6 2	3 3

Difference between gain in weight of patients in treatment and control groups

Initial weight less than 9 st	t=1 91, n=38, P=0 07
Initial weight 9 st or more	t=1 15, n=36, P>0 1
All patients	t=1 58, n=76, P>0 1

* Data for 1 patient unavailable

The effect of treatment on the patient's weight is shown in table VI Patients who were advised to stop smoking gained, on average, slightly more weight than those not advised to stop (7 5 lb against 6 2 lb) This was not due to the inclusion of fewer patients with a low initial body-weight in the treated group (noted in table I), because patients who were grossly underweight on admission tended to gain more weight than did other patients This factor has therefore reduced the difference between the groups which would have been observed if the initial weights of the two groups of patients had been more closely comparable Even so, the differences are small, and when the results for patients under and over 9 stone in weight are considered separately they are not statistically significant There is, however, a strong clinical impression that it is easier to gain weight after stopping smoking, and the present data provide some support for that belief

TABLE VII—EFFECT OF TREATMENT ON PATIENTS SYMPTOMS

Treatment	No of patients	Symptom-free throughout	Occasional pain or dyspepsia	Daily pain for a week or more
Advised to stop smoking	40	13	20	7
Not advised to stop smoking	40	18	15	7

Difference between proportions with and without symptoms in treatment group and in control group
χ^2=1 32, n=1, P>0 1

The results judged subjectively by the patients' symptoms are shown in table VII The special treatment was not usually started for four to six days after admission to hospital, and the symptoms complained of during the first week have therefore been ignored Table VII shows that fewer of the patients who were advised to stop smoking were completely free from symptons, but the difference is not significant, and the proportion who had major symptoms—i e, daily pain for a week or longer—was the same in both groups Possibly the attempted withdrawal of tobacco may have increased the patient's awareness of minor symptoms in a few instances, but the difference recorded may also have been a chance finding independent of the method of treatment

Discussion

The results of the inquiry into patients' smoking habits are difficult to interpret Several explanations are possible

(1) Perhaps the presence of an ulcer stimulated the desire to smoke The disease is a chronic one, and the recorded habits are not necessarily the same as those before the first symptoms appeared Some patients find that their symptoms are relieved by a cigarette, and some may have taken up smoking because of their ulcer If this were so, one would expect to find that the proportion of smokers who had begun late in life would be greater among the ulcer patients than among the controls The data on this point are inconclusive, but, so far as the group of patients is concerned for whom the association is greatest (i e, men with gastric ulcers), it seems that the converse may be true

(2) Some psychological factor might predispose to the development of an ulcer and also to the subject's becoming a smoker There are at present no data against which this hypothesis can be tested, but it is not inherently unreasonable Certainly it is widely believed that personality traits are related in some way to the development or the maintenance of duodenal ulcers and, to a less extent, of gastric ulcers

(3) Smoking might be the primary factor and might contribute directly to the production or the maintenance of some of the ulcers In this case it would be expected that the proportion of heavy smokers among the ulcer patients would be greater than among the controls That this was not so could, however, be explained if some patients had been advised to cut down their smoking as part of the treatment of their condition, or if they had themselves found that it was beneficial to do so

Taken by themselves the data obtained retrospectively from patients' smoking histories do not distinguish between these three hypotheses Taken in conjunction with the results of the clinical trial of the effect of stopping smoking, however, it seems probable that the third explanation—that smoking can sometimes be a factor in the production or the maintenance of a peptic ulcer—is the true one That the best results were obtained in those patients who stopped smoking completely is not in itself conclusive This might have arisen if the patients who stopped smoking were also more cooperative in other ways, or if they were able to do so through being mentally more relaxed But in this case, if the advice to stop smoking had not had any direct effect, it would be expected that the patients who did not stop would have done particularly badly. In fact, the patients who did not stop completely (but nearly all of whom substantially reduced their consumption) also fared better than the controls, who were not advised to stop smoking at all. The one observation that weighs against the conclusion is that the average degree of healing among those patients who were not smoking on admission was practically the same as that in the controls, who continued to smoke. If smoking hinders the healing of an ulcer, it might have been supposed that the rate of healing of the ulcer would have been greater among patients who were not smoking on admission than among smokers. It must be remembered, however, that the patients could not usually be admitted until several weeks after the presence of an ulcer had been diagnosed in the outpatient department, and by this time the ulcer was not infrequently healed. Since some patients gave up smoking on their doctor's advice before coming into hospital, it is not unreasonable to assume that ulcers which were still big enough to require treatment, despite the cessation of smoking, were, as a group, more resistant to treatment than average.

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* A patient was regarded as having stopped smoking during treatment if he smoked an average of less than 1 cigarette a day or less than $^1/_4$ oz. of tobacco a week

The conclusion that smoking can sometimes be a factor in the production or maintenance of a peptic ulcer accords with the results of three recent investigations. Doll and Hill (1956) studied the mortality of doctors in Britain, who had previously been classified according to their smoking habits, and found that the mortality from peptic ulcer was lowest among non-smokers (no ulcer deaths were observed in this group) and increased with the amount smoked to a maximum among smokers of 25 g. or more of tobacco a day. The total number of ulcer deaths (21) was, however, small, and the differences were not statistically significant. In the U.S.A. Hammond and Horn (1957), who studied a larger group, found that 8 of the 124 deaths attributed to peptic ulcer occurred among non-smokers, whereas the expected number, calculated from the age-specific death-rates for the whole group, was 16.8.† In this study the difference was well marked only for men with gastric ulcers (gastric-ulcer deaths in non-smokers 0, expected 7.0, duodenal-ulcer deaths in non-smokers 8, expected 9.8). The great majority of ulcer deaths occur, however, as a result of perforation, bleeding, or operation, and the fatality of these complications is largely influenced by the condition of the chest. It is therefore possible that the mortality from peptic ulcer is partly influenced indirectly by smoking, through the association of smoking with chronic chest disease, but, if this was so, it would be difficult to understand why the effect should be so much greater for gastric ulcers than for duodenal ulcers.

In the third study (Brown, McKeown, and Whitfield 1957), more than 1000 men aged 60–69 on the lists of eleven general practitioners were examined, and their smoking histories were recorded. The prevalence of peptic ulcer increased from 6.6% among the non-smokers to 8.3% among smokers of 1–9 cigarettes a day, to 9.2% among smokers of 10–19 cigarettes a day, and to 13.0% among smokers of 20 or more cigarettes a day.

It appears unlikely, however, that smoking is an important and direct cause of peptic ulcer. The consumption of tobacco, particularly of cigarettes, has increased in Britain over the past two or three decades, while the incidence of gastric ulcer is thought to have diminished. In contrast, the incidence of duodenal ulcer has almost certainly increased, but in this case the association with smoking is less. Furthermore the distribution of gastric-ulcer mortality throughout the world (Segi 1957) is quite unlike the distribution of tobacco smoking. On present evidence, therefore, it seems more reasonable to suggest, as a working hypothesis, that the effect of smoking is to interfere with the healing of the ulcer and to help to maintain its chronicity.

Summary

The smoking habits of patients with peptic ulcer are compared with those of a control group of patients with other diseases believed to be unrelated to smoking. Each ulcer patient was matched by two controls chosen to resemble the ulcer patients in their sex, age, place of residence, and (for male patients) their socio-economic class.

The percentage of non-smokers was less among the ulcer patients than among the controls both for gastric ulcers and for duodenal ulcers and in both sexes (1.3% among 235 men with gastric ulcers against 4.7% among the corresponding controls, 2.1% among 284 men with duodenal ulcers against 5.8%, 51.1% among 92 women with gastric ulcers against 66.8%, and 53.7% among 54 women with duodenal ulcers against 62.0%). In contrast, no appreciable differences were found between the proportions of heavy smokers.

More of the men with gastric ulcers than of their controls had begun to smoke before the age of 15 (19.8% against 14.1%), and less had begun to smoke at the age of 30 or more (17.7% against 23.9%). No important differences in the age at starting to smoke were found in the other groups. With both types of ulcer the proportion of smokers who smoked only cigarettes was higher in the ulcer group than in the controls (men with gastric ulcers 91.4% against 79.0%, men with duodenal ulcers 85.3% against 80.9%).

These results may be interpreted in several ways, therefore further evidence was sought in a clinical trial. Inpatients with gastric ulcers who, on admission to hospital, were regular smokers were divided at random into two groups. In one group the patients were advised to stop smoking, in the other they were given no such advice. All the patients were treated in bed for four weeks and all other treatments were prescribed equally in both groups.

Among 40 patients advised to stop smoking the ulcer healed by two-thirds or more in 30 (75%) and the average reduction in the size of the ulcer niche was 78.1%. Among 40 patients not advised to stop smoking the ulcer healed by two-thirds or more in 23 (58%) and the average reduction in the size of the ulcer was 56.6%. The ulcer healed by two-thirds or more in a higher proportion of those who followed the advice (19/22 or 86%) than of those who reduced their smoking but did not stop completely (11/18 or 61%), and the average reduction in the size of the ulcer was also greater in the former group (83.2% against 71.8%).

The average gain in weight and the severity of symptoms were not significantly different in the group of patients advised to stop smoking and in the controls.

The results accord with three recent studies of the mortality and morbidity of peptic ulcer in relation to smoking habits, and it is concluded that, in some patients,

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† Calculated from data given in a personal communication.

smoking interferes with the healing of a peptic ulcer and helps to maintain its chronicity

We are grateful to Miss Keena Jones, Mrs M M Glyn, Mrs B Kenchington, and Mrs R Bird, who recorded the smoking histories of the patients, and, in particular, to Miss Jones for assistance in the statistical analysis of the results

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DIAPHRAGMATIC HERNIÆ DUE TO BLUNT TRAUMA

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DIAPHRAGMATIC herniæ (apart from those through the œsophageal hiatus) may be traumatic or congenital As a result of two world wars, and the increase of road accidents, diaphragmatic hernia of traumatic origin is steadily becoming commoner (Carter et al 1951) We present five cases in which the diagnosis was made some time after the injury

Case-reports

Case 1—A boy, aged 12 years, was admitted in August, 1950, shortly after a motor accident in which he was hit in the side He was cyanosed and dyspnœic There were bruises over the scalp and right elbow, besides upper abdominal rigidity Skiagrams showed a subluxation of the right acromioclavicular joint and slight displacement of the right olecranon epiphysis, the X-ray film of the chest showed what appeared to be a high cupola of the diaphragm with partial collapse of the left lower lobe, and multiple large gas bubbles below it (fig 1) Traumatic diaphragmatic hernia was suspected, but fluoroscopy showed a paralysis of the left cupola The bone injuries were treated with Robert Jones strapping

The general condition improved, and further X-ray films of the chest showed a gradual return of the left diaphragm to a much lower position (fig 2*a*), but the collapse of the lower lobe persisted He continued to have pain in the epigastrium, left chest, and shoulder, relieved by resting, and dyspnœa on exertion A barium-meal examination confirmed the earlier diagnosis of traumatic diaphragmatic hernia, and showed the main body of the stomach (which had undergone volvulus) in the left lower chest (fig 3) Unfortunately, the boy was lost sight of till October, 1951, when he came into hospital with increasing symptoms He also complained of "fluid splashing in the chest" when he ran The left lower chest was hyperresonant anteriorly Breath sounds were diminished over this area, gurgling could be heard

At left thoracotomy, a large amount of small gut and transverse colon, as well as the stomach, were found in the left chest There was a rent in the left diaphragm, 10 cm long, parallel to the lateral chest wall, and running forwards from just in front of the œsophageal hiatus there were a few adhesions at the anterior end of the rent The gut was returned to the abdomen with some difficulty, and the hole repaired with nylon The postoperative course was smooth

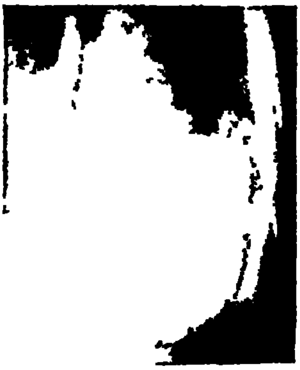


Fig 3—Case 1: Barium-meal examination

In this case, though traumatic diaphragmatic hernia was suspected early, hasty interpretation of the fluoroscopy findings led us astray The lateral view of the chest film taken two months after the accident (fig 2*b*) shows that what was presumed to be a high cupola was in fact the upper margin of the herniated stomach, the arch-like shadow falls short of the anterior chest wall anteriorly

Case 2—A man, aged 43, was admitted to the Royal Infirmary in September, 1952, with epigastric distension after

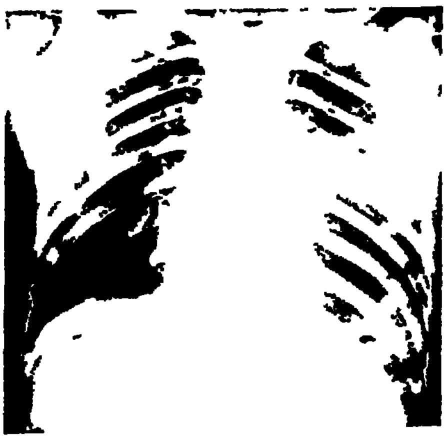
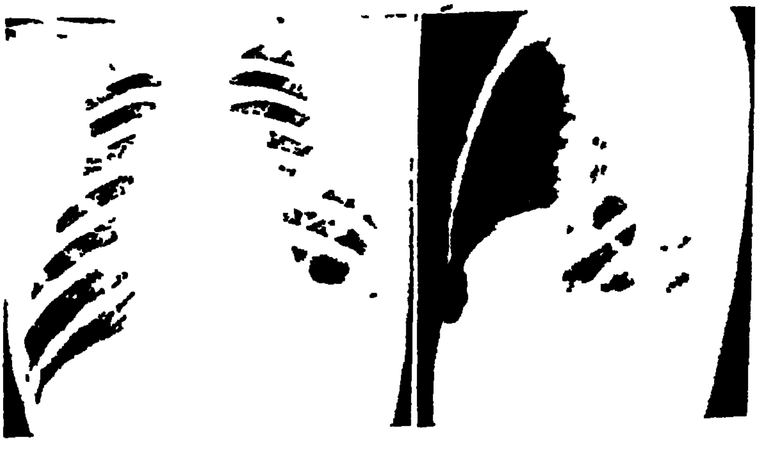


Fig 1—Case 1 Posteroanterior view of the chest soon after the accident, showing the collapse of the left lung and areas of translucency in the left lower chest



(*a*) (*b*)

Fig 2—Case 1 Posteroanterior (*a*) and left lateral (*b*) views of the chest a few months after the accident Although the left lung is better expanded the gas bubbles in the left chest persist

food, worse on lying down. He had been buried by a fall of coal in a mine in August, 1951. Since the accident, he had had epigastric fullness soon after a meal, partly relieved by vomiting. Dieting gave very little relief. Clinical examination showed a hyperresonant zone in the left lower chest. Barium meal and follow-through confirmed the diagnosis of diaphragmatic hernia.

At left thoracotomy, the stomach, spleen, and omentum were found to have herniated through a rent, 20 cm. long, across the left cupola, extending posteriorly up to the crura. The abdominal viscera, including the spleen, were returned to the abdomen, and, after the edges had been freshened, the rent was repaired with interrupted silk. Postoperative progress was uneventful.

Case 3.—A man, aged 28, was first seen in July, 1957, complaining of epigastric fullness and pain after food, worse on reclining. He had been involved in a motor-cycle accident four years previously, when he sustained simple fractures of both bones of the left forearm, and a fractured pelvis. The epigastric pains had come on a year later. Clinically, there was no abnormal physical sign in the chest or abdomen. A barium-meal showed a diaphragmatic hernia, the stomach, which had undergone a volvulus, was in the left hemithorax (fig. 4).

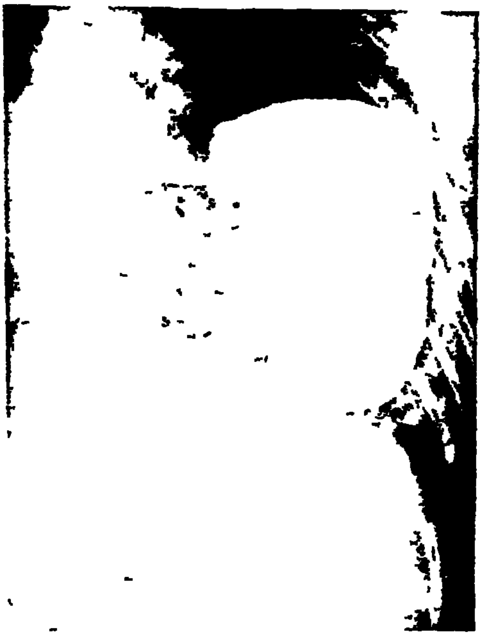


Fig. 4—Case 3. Barium-meal examination shows the volvulus of the stomach inside the left chest with the cardia and the pylorus still below the level of the diaphragm.

At left thoracotomy, the stomach, left lobe of the liver, small gut, and omentum were found to occupy the left chest, they were attached to the rim of the rent across the left cupola. These organs were freed, and returned to the abdomen. The rent was repaired with interrupted silk sutures. The postoperative course was without incident.

Case 4.—A man, aged 33, was first seen in September, 1942, because of epigastric pains (chiefly soon after meals, and sometimes after exertion), and severe eructations. The epigastric pains had come on soon after a fall in January, 1942. Clinically, nothing abnormal was found in the chest or abdomen. A skiagram of the chest showed the left diaphragm obscured by dark shadows, " not unlike distended bowel " in the left lower chest. A barium-enema examination showed these shadows to be due to the splenic flexure of the colon lying above the level of the diaphragm.

At left thoracotomy, the splenic flexure of the colon was found in the left chest, having come through a rent across the left cupola. The colon was returned to the abdomen, and the rupture repaired. Further progress was smooth.

Case 5.—A man, aged 27, was buried by a fall of coal in a colliery in January, 1940, and treated in a plaster-of-paris cast for a spinal injury. Soon after the accident, he started having sharp pains in the left anterior chest and epigastrium, worse on exertion or bending, and after meals, this was associated with shortness of breath as well. When we first saw him in September, 1949, the chest and the abdomen appeared normal clinically. An X-ray film of the chest had revealed the stomach in the left chest (fig. 5), with a large fluid level, a barium meal confirmed this. The stomach had undergone volvulus.

At left thoracotomy, the left chest was found to contain the stomach, spleen, coils of small intestine, and the splenic flexure of the colon. There was a rent in the diaphragm, right across the cupola, lateral to the œsophageal hiatus. The abdominal organs were returned to the addomen, the margins of the rent were freshened, and the diaphragm was repaired with nylon. The immediate postoperative course was marred by a segmental collapse in the right lower lobe.

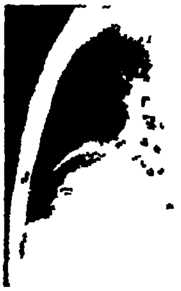


Fig. 5—Case 5. Left lateral view of the chest 7 years after the accident, confusion with localised eventration of the diaphragm is easy.

Discussion

The diaphragm, along with the transversi sterni et abdominis and the levatores ani, is primarily a compressor of the cœlomic cavity. Its respiratory function is of only secondary significance (Wood Jones 1946). Therefore it is reasonable to expect all the compressors to take the strain at the moment of impact, when a sudden compression force is applied to the lower chest or upper abdomen or both. The bursting force is expended on the relatively mobile diaphragm, whose periphery (the costal element) is protected by the lower thoracic cage, hence it is the cupola that splits—at or near the musculotendinous junction, as in rupture of other muscles. The right dome is well protected by the solid and elastic liver, while the left one has no such protective buffer—on the contrary, it is weakened because the left leaf of the central tendon is small, and the musculotendinous junction is sited across the very vertex of the cupola. The rent rarely if ever runs backwards into the œsophageal hiatus, for the crural sling has a tendency to pull away into the comparative safety afforded by the lumbar spine. If the rent is large, massive herniation of the abdominal viscera follows, giving rise to immediate symptoms. With small rents (which are commoner with penetrating injuries), omentum may plug the hole, which later enlarges, helped by associated infarction of the diaphragm at the time of the original accident. Strangulation is the catastrophic sequel to these lesser deficiencies. A subsequent trivial trauma, which increases the intra-abdominal pressure facilitates this process. Carter and Giuseffi (1948) found that 90% of strangulated diaphragmatic herniæ were traumatic in origin.

Clinical Types

Immediately after trauma.—Besides signs of shock, there may be epigastric pain and distress, radiation of pain to the shoulder—dyspnœa, and cyanosis (as in case 1). Physical examination may show a contralateral mediastinal shift, dullness or hyperresonance will be evident in the involved hemithorax There may or may not be symptoms and signs of incarceration of gut

Latent group—The symptoms are vague and bizarre, with periodic bouts of epigastric distension and dyspnœa, relieved by vomiting

Strangulated herniæ—The signs and symptoms are the same as in strangulated congenital diaphragmatic herniæ, signs of strangulation, without obvious evidence of the site, are the rule The early symptoms are pain in the upper abdomen or lower chest, vomiting, and hiccups Upper abdominal rigidity is soon evident, but abdominal distension is never great The closed-loop obstruction inside the chest leads to rapid distension, and a bloodstained pleural effusion Deterioration of the general condition is equally rapid, with increasing dyspnœa The radiographic appearances are equally confusing

Radiographic Appearances

The common findings are

1 Contralateral mediastinal shift,

2 High "cupola" (actually the upper margin of the herniated gut simulating an exaggeratedly high diaphragm),

3 Abnormal gas-bubbles or solid-viscera shadows in the hemithorax, and

4 Areas of collapse in the adjacent lower lobe

Fluoroscopy may "confirm" the mistaken diagnosis of paralysed diaphragm Barium-meal or enema examination or both will clinch the diagnosis, and make easy the differentiation from eventration of the diaphragm, subphrenic abscess, and pleural effusion

Treatment

The treatment of traumatic diaphragmatic herniæ is surgical, when they are complicated by strangulation, urgent operation is mandatory The transthoracic approach is ideal, because it leads one directly to the involved area, further, as the herniated viscera are always adherent to the diaphragm or the lung, mobilisation under direct vision is possible, and, last but not least, accurate repair is easy, after freshening up the edges Interrupted non-absorbable sutures are used In strangulation necessitating resection of gut, the thoracic approach is just as easy as the abdominal But, where colon is strangulated, the possibility of twin-loop obstruction should be borne in mind—the cæcum and ascending colon distal to a competent ileocæcal valve act as a second closed loop, rapidly distend, and are in imminent danger of perforation, unless recognised early It may be necessary to extend the rent in the diaphragm radially, to free the incarcerated viscera

Summary

Five cases of diaphragmatic herniæ, caused by blunt trauma and treated by surgery, are described One illustrates how easily, on X-ray films and fluoroscopy, herniated viscera may be mistaken for a high diaphragm

The treatment is surgical In strangulation, operation is urgent

We are grateful to Dr J Wilkie (Royal Infirmary) and Dr E K Abbott (City General Hospital) for the radiographs and interpretations

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ANTI-GLOBULIN CROSS-MATCHING TEST
ITS USEFULNESS FOR URGENT BLOOD-TRANSFUSIONS

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As the use of blood-transfusion increases, more and more patients develop specific immune isoantibodies If a patient requires a blood-transfusion very urgently, is it worth while to try to detect incomplete antibodies by a short-cut anti-globulin cross-matching procedure, or must one take a chance and give blood matched only for ABO compatibility or, to patients in extremis, unmatched group-O Rh-negative blood?

Ideally, a cross-matching test should include a tube test for ABO compatibility carried out by mixing at room temperature the patient's serum and a saline suspension of the donor's cells, and an anti-globulin (Coombs) cross-matching test carried out at 37°C The saline matching test can be done without long standing if the tubes are centrifuged at slow speed to allow closer contact of antigen and antibody (Jennings 1954, Grove-Rasmussen et al 1954) Thus a saline cross-match can be read, employing centrifugation, in 5–30 minutes A direct matching at 37°C of the patient's serum and the donor's cells suspended in serum or albumin is probably unnecessary if the anti-globulin cross-matching is done However, the anti-globulin cross-matching is usually considered to need incubation at 37°C for at least 1 hour, preferably 2 hours, before testing with suitable dilutions of anti-human-globulin serum

The present investigation was undertaken to find out how far one can shorten the incubation time without missing dangerous circulating antibodies Sixty-nine antisera were tested to determine the time required for red-cell sensitisation and the factors which affected the speed and degree of sensitisation

Procedure

Sera

The following human sera, containing incomplete and occasionally in addition low-titre complete, antibodies were tested 30 anti-D, 6 anti-C, 3 anti-c, 4 anti-E, 1 anti-e, 4 anti-Le^a, 11 anti-K, 8 anti-Fy^a, 1 anti-S, and 1 anti-Jk^a Some of the sera were fresh, most had been stored at −20°C for periods of up to 2 years

Anti-globulin (Coombs) Test

The anti-globulin cross-match was carried out as recommended by Dacie (1956) One drop of a 30% cell suspension in saline solution was added to 4 drops of serum, undiluted or diluted (see below), in an 8 mm test-tube, and placed in a water-bath at 37°C for 1, 5, 15, 30, 60, or 120 minutes After the prescribed time of incubation the tubes were removed from the water-bath and the cells washed three times with a large volume of saline at ordinary room temperature

After the saline had been decanted and washed, the cells were resuspended in the remaining saline, making an approximately 30% suspension One drop of this suspension was then mixed, on an opalescent tile, with one drop of suitably diluted anti-globulin serum, rocked gently for 5 minutes, and then inspected over a strong light without the aid of magnification The reactions were scored as follows +, just detectable granularity, ++, uniform easily visible granularity, +++, granularity with moderate aggregation into clumps, ++++,

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coarse clumping throughout; + + + +, aggregation into a few solid masses of red cells For the purpose of this work, the minimum time for sensitisation was taken as that giving at least + agglutination

Serum and cell controls were set up with each batch to check the specificity of the reaction and the avidity of the anti-globulin serum

Dilution of Test Sera

The strength of the antibodies in each serum was determined by serial dilution with fresh group-AB serum stored at −20 C and then by incubating for 2 hours Each serum was then tested undiluted and at the maximum dilution giving detectable sensitisation, the reciprocal of this dilution being recorded as the titre. Dilutions were made with AB serum so that the protein concentrations and complement activity would be more constant In the case of the Lewis antibodies dilutions were made with fresh compatible Le^{a-b-} serum

Dilution of Anti-globulin Serum

The dilutions of the anti-globulin serum used were those determined to be optimal for the particular batch, by testing against cells sensitised by a weak and by a strong anti-D serum (Rosenfield et al 1951) and by a serum containing anti-Le^a (Mollison 1956)

A single rabbit anti-human-globulin serum was used throughout the tests This had been prepared by hyper-immunising a rabbit by repeated injections of whole human serum (Dacie 1956) The activity of this serum was compared with that of several other anti-globulin sera used routinely in other laboratories, to show whether or not it could be considered an " average " reagent.

Red Cells

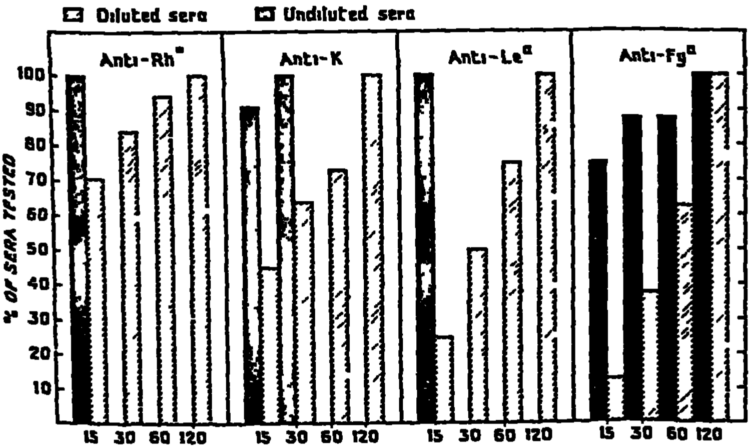
The cells used for sensitisation were collected into acid citrate dextrose (A.C.D.) and stored at 4°C for not more than 72 hours The cells were washed once in saline just before use, before being made into a 30% suspension

To determine whether the speed of sensitisation was affected by the age of the cells, duplicate tests were set up with fresh (less than 4 hours old) and three-week-old cells from the same donors taken into acid citrate dextrose solution and stored at 4 C in pilot bottles

Results

The times required for sensitisation with the various antibodies tested are summarised in the accompanying figure

Anti-D (30 sera)—All the anti-D sera, which varied in titre from 1 to 1024, sensitised D-positive cells after 15 minutes' incubation, and all but five gave at least + agglutination after 5 minutes' incubation The shortest incubation time tried (1 minute) produced detectable sensitisation when high-titre anti-D sera were used When the sera were diluted maximally with AB serum (see above), the time required for + sensitisation was much more variable 71% of the sera gave positive results after only 15 minutes' incubation, but 29% required more than 15 minutes and 5% required 120 minutes' incubation.



* Includes all Rh types

Percentage of sera sensitising appropriate red cells at various incubation times when used undiluted or diluted.

Rh sera other than anti-D (14 sera)—With Rh antibodies other than anti-D the results were similar to those with the D-sensitised cells With undiluted serum, sensitisation was detectable after 5 minutes' incubation with all except four sera which had titres of 1, these required 15 minutes' incubation When the sera were maximally diluted, sensitisation was slower, as with anti-D sera four sera sensitised cells after 5 minutes' incubation and nine after 15 minutes' incubation, and the remaining five required up to 120 minutes

Anti-K (11 sera)—Sera containing anti-K at titres of 2–64 were somewhat slower in sensitising However, eight " coated " K-positive cells after 5 minutes' incubation, and ten after 15 minutes' incubation One, having a titre of 2, required 30 minutes' incubation Maximally diluted, five of the sera required over 15 minutes' and three required 2 hours' incubation

Anti-Le^a (4 sera)—With undiluted sera containing anti-Le^a, all the Le^a-positive cells tested gave + reactions within 15 minutes With sera maximally diluted with compatible Le^{a-b-} serum sensitisation was rather slow, three of the sera needing 30–60 minutes

Anti-Fy^a (8 sera)—Sera containing anti-Fy^a were the slowest in producing sensitisation Two, having titres of 1 and 2, required over 15 minutes for a + reaction When maximally diluted, five of the sera required 60 minutes or more for sensitisation

Anti-S and anti-Jk^a (1 serum of each type)—Both sera had titres of 4, each coated appropriate cells after 15 minutes' incubation Both were slow when maximally diluted, and required 1–2 hours' incubation to give + reactions

Age of red cells—No significant difference in sensitisation time between fresh and three-week-old cells was detected with anti-D, anti-Fy^a, or anti-Le^a With sera containing low-titre anti-K, six required 30 minutes or more for sensitisation when the cells were three weeks old, whereas only two of the sera needed more than 15 minutes' incubation with fresh cells

Comparison of Anti-globulin Sera

The criteria used for comparison of anti-globulin sera were the titre, whether they gave a prozone, the strength of the reactions against weakly and strongly sensitised D-positive cells, and the strength of the reaction with cells sensitised with anti-Le^a Some of these anti-globulin sera were prepared from rabbits, and others from goats

When the sera were tested for reactions with cells sensitised by anti-Le^a and anti-D they reacted similarly to the anti-serum used in this investigation (Crawford and Mollison 1951, Dacie 1951, Cutbush et al 1955) Although the titres of the anti-globulin sera varied considerably, each gave a + + + + reaction with D-positive cells sensitised with a strong anti-D serum, and a + to + + reaction with cells sensitised with a weak anti-D serum, when used at the recommended dilution The greatest variation was seen in the ability of the anti-globulin sera to detect antibodies, such as the anti-Le^a, which may bind complement (Dacie et al 1957) The two commercially prepared anti-globulin sera tested did not detect this type of antibody satisfactorily

Discussion

The results show that 97% of the sera, when tested undiluted, caused cells containing the appropriate antigens to be definitely agglutinated by an anti-globulin serum after 15 minutes' incubation On the grounds that the sera used were not representative of antibody-containing sera as a whole, in that they had, with the exception of the anti-D sera, been selected for storage because they contained an antibody of useful titre, they were maximally diluted with AB serum to simulate weak antibodies When diluted in this way, 48% of the sera required from 30 minutes' to about 2 hours' incubation to sensitise the appropriate cells sufficiently to give + agglutination However, with the exception of the two anti-Fy^a sera and one anti-K serum, the dilution next below the maximum gave + sensitisation in 15 minutes or less

Factors Influencing Speed of Sensitisation

All the sera having antibody titres of over 2 sensitised appropriate cells after 15 minutes' incubation Sera with antibody titres of 2 or 1, and sera diluted maximally with AB serum, varied considerably as regards the required time of incubation As would be expected (Mollison 1956), the variation of avidity of the sera was greatest in those containing antibodies other than the Rh group

Wootton (1951) showed that cell sensitisation improved if the relative volume of serum to cells was increased and there was frequent agitation to ensure good contact with antigen and antibody With shortened incubation times it is particularly important to have at least four volumes of serum to one of cells The incubation time required for + sensitisation with low-avidity or low-titre antibodies could be shortened if the volume of serum was increased to 20 drops, provided there was adequate mixing and the temperature of the mixture was brought quickly to 37°C in a water-bath Addition of serum beyond a ratio of 20 1 did not further diminish sensitisation time

The importance of using fresh unheated complement-containing serum has been emphasised in relation to sensitisation by antibodies such as anti-Lewis and anti-Kidd (Mollison and Cutbush 1955, Dacie et al 1957)

Age of Red Cells

The age of the red cells did not appear to be significant except with anti-K, when storage of the cells in A C D for 3 weeks affected not only the apparent titre of the serum but also the speed of sensitisation The Kell antigen is known to be labile, particularly if the cells are kept as a clot (Grove-Rasmussen et al 1954) Although the antigen is better preserved in A C D (Dunsford and Bowley 1955), this study shows that its preservation is still not entirely satisfactory

Anti-globulin Serum

For optimal detection of sensitisation on the tile, an anti-globulin serum should be used which has been shown to detect sensitisation by antibodies such as anti-Le^a, as well as anti-D At least two dilutions of anti-globulin serum should be used to avoid the dangers of a prozone and to pick up antibodies other than Rh, which are often better agglutinated in a higher concentration of anti-globulin serum Each batch of anti-globulin serum should be tested to determine the optimal concentration for detecting cells weakly and strongly sensitised by an anti-D serum, and cells sensitised with an anti-Le^a serum

Enough time should be allowed for the reaction between anti-globulin serum and sensitised cells to take place Cells sensitised with anti-Fy^a were particularly slow to undergo agglutination, and with weak reactions as much as 10 minutes' rocking was required for agglutination to become maximal

As previously stated, a + reaction was used as an end-point for determining the time required for sensitisation Any agglutination is, of course, significant in reading a cross-matching test and must be taken as evidence of incompatibility, providing the controls are negative

Conclusion

The answer to the question posed at the beginning of this paper—Is a short-cut anti-globulin cross-matching procedure of any value when blood is needed urgently ?—seems to be Yes If the patient can wait 30 minutes for blood, a cross-matching procedure, with 15 minutes' incubation, can be completed which will detect nearly all dangerous antibodies

The low-titre antibodies that may be missed by the shortened incubation time do not usually give rise to severe fatal hæmolytic transfusion reactions However, that the rate of destruction of incompatible red cells is not completely related to the titre of the antibody has been shown by Mollison and Cutbush (1955), who injected small volumes of ^{51}Cr-tagged incompatible red cells into patients with various antibodies and found that the disappearance seemed to depend not only on the strength of the antibody but also on its nature and specificity More recently, Fudenberg and Allen (1957) have described two rare cases of severe hæmolytic transfusion reactions in patients whose antibody was not demonstrable until after the offending transfusion Their studies with ^{51}Cr-tagged red cells indicate that even in the absence of detectable circulating antibody incompatible red cells may be destroyed very rapidly

These findings lend added weight to the already appreciated dangers of blood-transfusions and emphasise the limitations of our present cross-matching technique Clearly, the use of shortened incubation times for the anti-globulin cross-matching slightly increases the hazard of transfusions Nevertheless such tests seem well worth applying in urgent cases when a delay of 15–20 minutes is permissible Even so, an additional anti-globulin cross-match should be set up so that a definitive reading can be made after 2 hours' incubation

No attempt was made to compare results of the anti-globulin cross-matching test using shortened incubation times with other rapid cross-matching procedures carried out in tubes or on tiles Though each of these methods has its own advantage, none seems to equal the anti-globulin test from the point of view of the variety of different antibodies detected

Summary

The efficacy of an emergency cross-matching procedure for incomplete antibodies, using the anti-globulin (Coombs) method, was investigated Sixty-nine sera containing incomplete antibodies of the Rh, Kell, Lewis, Duffy, S, and Kidd systems were tested undiluted and diluted so as to simulate low-titre sera in order to determine how quickly the cells became detectably sensitised

97% of the sera used undiluted sensitised the appropriate cells after 15 minutes' incubation in a water-bath at 37°C 39%, when maximally diluted, were still able to sensitise cells after 15 minutes' incubation, 61%

of these diluted sera needed between 30 and 120 minutes' incubation

It is concluded that the shortened (15-minute-incubation) anti-globulin cross-matching test is well worth carrying out

I wish to thank Prof J V Dacie for his advice and encouragement, Dr A E Mourant, of the Lister Institute, and Mr I Dunsford of the Sheffield Blood Transfusion Service, for supplying antisera and anti-globulin for testing, and Dr L Sacker for supplying anti-globulin sera

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FERRITIN IN NUTRITIONAL ŒDEMA

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It is well known that œdema often complicates malnutrition, but its pathogenesis is not clearly understood Starling's classical concept whereby physicochemical alterations resulting from the changes in the plasma-proteins were held responsible for the œdema is now recognised as inadequate Gopalan (1950) observed increased excretion of an antidiuretic substance in the urine of patients with nutritional œdema and oliguria The response of such patients to a water-load was impaired, and so was that of laboratory animals on low-protein diets (Gopalan and Ramanathan 1957, Dicker et al 1946) Normal liver was shown to be capable of inactivating the posterior-pituitary antidiuretic hormone (Eversole et al 1949), and this capacity was found to be impaired by low-protein diets (Birnie 1950, Gopalan et al 1953) On the basis of these observations a tentative hypothesis to explain the pathogenesis of œdema was put forward by Gopalan and Venkatachalam (1952) and Gopalan (1955)

Baez et al (1950) showed that the iron-protein complex ferritin can in certain circumstances exert a considerable antidiuretic effect, and that this is mediated through the stimulation of the posterior pituitary Ferritin is stored mainly in the liver and spleen, which under certain conditions release measurable amounts of it into the circulation The presence of such ferritin in the blood-stream has been reported in some clinical states—e g , congestive heart-failure, toxæmia of pregnancy, hepatic cirrhosis, and the nephrotic syndrome (Shorr et al 1950)—which are all characterised by periods of oliguria and altered water metabolism

We have no information, however, on whether this potent antidiuretic agent is present in the blood of patients with œdema associated with protein and calorie undernutrition Profound structural and functional changes are known to take place in the liver as a result of malnutrition, and œdema is often an associated factor. It is important, therefore, to determine whether the œdema of undernutrition is mediated through the release of ferritin from the damaged liver into the circulation

MESOAPPENDIX ASSAY FOR FERRITIN

Case no	Clinical condition	On admission	10–14th day (no clinical œdema)	One month after end of therapy
1	Kwashiorkor	+	–	–
2	,,	+	–	–
3	,,	+	+	–
4	,,	+	–	–
5	,,	+	+	–
6	,,	–	–	–
7	Nutritional œdema in adult	+	–	–
8		+	–	–

The Investigation

The patients studied were six children with kwashiorkor, and two adults with nutritional œdema The clinical features of such cases have already been described (Venkatachalam et al 1954, Gopalan et al 1952)

Peripheral venous blood of these eight patients was collected, with heparin 2 mg per ml as the anticoagulant The plasma was separated by centrifugation and assayed on the same day for the presence of biologically active ferritin, using the rat-mesoappendix test of Zweifach (1948) The test is based on the observation that ferritin has a vasodepressor effect on the constrictor response of small blood-vessels to topically applied adrenaline The test is very sensitive and can detect 0 001–0 002 µg of ferritin nitrogen per millilitre This technique has been satisfactorily employed for detecting vasotropic substances in several previous investigations (Srikantia et al 1956, Baez et al 1955, 1956)

In all cases where a vasodepressor response was obtained with this test, the fact that this effect was due to the action of ferritin and not to some other vasotropic substance was established by the use of antiferritin serum 0 9 ml of the plasma that gave a positive vasodepressor test was mixed with 0 1 ml of antiferritin serum and incubated at 37°C for twenty minutes, 0 5 ml of this was again assayed for vasodepressor activity, and none was found

The assays for ferritin in the plasma of the eight patients were done at the height of the œdema, at ten to fourteen days after start of treatment with a high-protein diet, and a month after the beginning of such treatment

Five of the six children with kwashiorkor and both of the adults with nutritional œdema had ferritin in their circulating blood on admission Only two of the six children had ferritin in their blood after clinical œdema had disappeared In all the cases ferritin was absent after a month of high-protein therapy

Comment

The presence of ferritin at a stage when oliguria and œdema are conspicuous, and its absence after nutritional therapy, appear significant It is tempting to postulate, in malnutrition, a causal relation between ferritinæmia and antidiuresis The evidence, however, is still only circumstantial Experiments are now in progress to elucidate the precise role of this antidiuretic agent in the pathogenesis of nutritional œdema

I wish to thank Dr C Gopalan, deputy director of the Nutrition Research Laboratories, Coonoor, for valuable advice in the conduct of the investigation and in the preparation of this note The anti-ferritin serum was kindly supplied by Dr S Baez and Dr A Mazur of the Cornell University Medical College and New York Hospital

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ANAEROBES IN ROUTINE DIAGNOSTIC CULTURES

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IN many hospital laboratories cultures are made in air as a routine, and the specimen is not investigated for anaerobes unless there is some special indication Logically the reverse procedure would be more reasonable, because strict anaerobes are very common and strict aerobes are very rare in medical bacteriology

Anaerobic culture is neglected partly because many pathogens which cause acute illness grow well in air and partly because of technical difficulties Plate cultures are as essential for the satisfactory investigation of anaerobes as they are for aerobes, and this means that a jar of some kind is required Recently the McIntosh and Fildes jar has been so modified that it is much simpler and quicker to use, and if anaerobic cultures are desirable there is no longer any technical reason why they should not be included routinely

Frequency of Anaerobes

For some years we have cultivated most specimens on blood-agar incubated in air and anaerobically Detailed records of cultures during the past six years have been examined to discover what would have been missed if specimens had been cultivated in air only

Anaerobes can almost always be isolated from fæces, from the vagina, and from the upper respiratory tract, therefore specimens likely to be contaminated from these sites during sampling have been excluded from this investigation Swabs sent from the dermatology department and swabs of chronically discharging ears have also been excluded This leaves specimens from tissues and fluids which are normally sterile, and therefore all the microbes isolated are considered to be potential pathogens

Methods

All specimens are first smeared on sterile glass slides and are then seeded on 10% defibrinated horse-blood agar in two plates and into Robertson's cooked-meat broth One plate is incubated in air, or in air plus 5–10% CO_2, and the other anaerobically (This is not as extravagant as it appears, because except in special circumstances two specimens are seeded on each plate making one whole plate per specimen) The cooked-meat broth is included as a means of isolating aerobes and anaerobes from scantily infected discharges, because it can be more heavily seeded than blood-agar It is also valuable because inhibitors in the pus are diluted and microbes can sometimes be recovered from the cooked-meat broth when antibiotics have inhibited their growth on the original plate cultures It is never used, however, as the sole primary medium for anaerobes To do so would be as unreasonable as to use a liquid medium for the primary isolation of aerobes When a satisfactory growth is obtained on the original plates and all types of organism seen in the smear are accounted for, the cooked-meat broth is discarded without subculture If primary anaerobic plate cultures cannot be made—for example, when a swab is cultured by inexperienced staff at night—it is left in transport medium (Moffet et al 1948), which was originally used for the preservation of gonococci but which also preserves other delicate microbes, including anaerobes, very effectively Since it is non-nutrient there is no danger that small numbers of a lusty species will outgrow a more important but more delicate species before plate cultures can be made

When appropriate, other selective media are used, but these three primary cultures are never omitted They are examined after overnight incubation and again on the 2nd day Incubation for at least 48 hours is vital because most of the anaerobes encountered do not appear on the 1st day, and a few take about a week to grow When cultures are sterile for no good reason after 48 hours' incubation, or when organisms seen in the smear have not appeared, the original plates are reincubated for 7 days The cooked-meat broth is subcultured, whether growth is apparent in it or not, on to blood-agar incubated in air and anaerobically and these plates are also incubated for 7 days In most cases it is possible to send a written report on the 2nd day

The recently modified McIntosh and Fildes jar * is made of tinned copper The capsule contains a catalyst which acts in the cold without electric or other activation A side arm holds an external indicator The lid is sealed by a gasket with a replaceable rubber ring Anaerobic plate cultures can be set up in 5 minutes

By this method microbes seen in the stained smear of the specimen can almost always be isolated Some samples of pus in which no microbes can be seen do remain sterile, and there are several possible reasons for this It may be because the infection was tuberculous, or caused by a microbe (such as the pleuropneumonia-like organisms) which cannot easily be seen in stained films (Stokes 1955) It may be due to the action of enzymes in the pus, which have destroyed the microbes before they could be cultivated, it may be due to the oxidation of delicate anaerobes which cannot grow if they are exposed to the air for a short time, and finally it may be due to faults in technique, the most common being overdrying of the blood-agar and leaking anaerobic jars

The term anaerobe as used here needs explanation Any organism is considered to be an anaerobe if, when seeded comparably on blood-agar, incubated in air plus 5–10% CO_2 and anaerobically, it appears on the anaerobic but not on the aerobic culture No further tests are made of its ability to grow in reduced concentrations of oxygen Carbon dioxide is added to the atmosphere in all anaerobic jars because it improves growth in some cases, 2% is sufficient, and should not be exceeded because higher concentrations inhibit some anaerobes (Hayward 1947) Differentiation between obligate anaerobes and CO_2-dependent organisms therefore requires that the aerobic cultures be incubated in a CO_2-enriched atmosphere

Results

Of 5394 specimens cultivated, 265 were sterile without a satisfactory explanation and 4737 yielded growth Of these, 496 yielded anaerobes and from 139 of them the anaerobes were in pure culture

The omission of anaerobic culture as a routine would have resulted in an increased number of specimens reported " sterile " In different years this increase would have varied from about 25% to nearly 100%

The common presence of anaerobes is not confined to any particular type of specimen Table I shows the results obtained from different kinds of infected material, from every type of specimen anaerobes were recovered at one time or another

The pleural fluids in table I all showed evidence of infection in the cell count One was a tuberculous empyema with a superadded anaerobic infection Of the anaerobes isolated from the blood, three were from cases of puerperal sepsis, three from subacute bacterial

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* The jar is obtainable from Baird and Tatlock (London) Ltd

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TABLE I—ANAEROBIC STRAINS ISOLATED FROM VARIOUS SOURCES

Specimen	Positive cultures	Total no yielding anaerobes	Anaerobes in pure culture	Percentage yielding anaerobes
Pleural fluid *	144	18	10	12 5
Cerebrospinal fluid *	33	3	2	9 0
Blood *	85	9	8	10 5
Abdominal pus	528	173	30	32 7
Genital pus	220	69	24	31 3
Neck lymph gland	101	8	3	8 0
Infected sebaceous cyst	66	21	13	31 0
Boils, &c	1339	18	4	1 3
Other	2221	177	45	7 9

* Details of culture methods are to be found in my *Clinical Bacteriology* (London, 1955)

endocarditis, two from pyrexia of unknown origin, and one in a mixed culture from a patient with a paracolic abscess whose history is given below Clostridia were isolated from the blood only twice The positive cultures from cerebrospinal fluid were all secondary to subacute otitis media, one of these infections was fatal In only two of all these specimens were anaerobes suspected before cultures were made

Anaerobes are common in the abdomen These specimens include abdominal-wall abscess, pelvic abscess, appendix abscess, and swabs of peritoneal fluid in peritonitis Most mixed cultures yielded a heavy growth of anaerobes, in more than half of them anaerobes were predominant

"Genital pus" includes samples from freshly opened pyosalpinx, Bartholin's abscess, and ischiorectal abscess The proportion of anaerobes is about the same as in abdominal pus but pure cultures are commoner

Lymph-glands of the neck are considered separately, because in the absence of any other growth they are often thought to be tuberculous Anaerobes can secondarily infect tuberculous abscesses, but the eight encountered here were investigated for tuberculosis and proved negative

Infected sebaceous cysts yield a high proportion of anaerobes They are almost all anaerobic cocci Some are large and in pairs and closely resemble staphylococci under the microscope, others are streptococci Sometimes they are accompanied by anaerobic fusiform bacilli (bacteroides)

"Boils, &c," includes breast abscesses and infections of the finger, which are almost always stahpylococcal Two of the four pure cultures were from breast abscesses, one was from a boil (probably an infected sebaceous cyst misdiagnosed), and the fourth was a paronychial infection

"Other" includes wounds of limbs and elsewhere and specimens sent with no indication of the site from which they came Most of these were probably from boils

Table II shows the frequency of isolation of different anaerobic species

The gram-positive cocci can be further differentiated (Thomas and Hare 1954), but this is time-consuming and as yet of little clinical importance since classification by biochemical tests cannot be correlated with pathogenicity They are therefore reported as anaerobic streptococci if chains are seen and as anaerobic gram-positive cocci if no chains are formed

TABLE II—NO OF ANAEROBIC STRAINS IN PURE AND MIXED CULTURE

—	Total no of specimens	Total no of strains	Gram-positive cocci	Fusiform bacilli bacteroides)	Clostridia	Other
Mixed culture (aerobes present)	357	473	208	206	29	32
Pure culture	139	169	100	59	5	5

Fusiform bacilli are also left undifferentiated for the same reason

"Gram-positive cocci" (table II) includes those which form chains and those which do not All but two of the clostridia were *Clostridium welchii* "Other" includes gram-negative cocci (veillonella), anaerobic diphtheroid bacilli, and lactobacilli

Discussion

These results almost certainly fail to reveal the real frequency of anaerobes in clinical specimens submitted for bacteriological examination Failures to detect their presence are inevitable in a busy hospital laboratory where some of the work has to be done by relatively inexperienced staff Moreover, the anaerobic jars used in this investigation were inferior to the more modern type now available

Anaerobes have long been known to form a large part of the normal human flora, and finding them frequently in pus is no new discovery For instance, Veillon and Zuber (1898) noted that anaerobic fusiform bacilli were the commonest organism in acute appendicitis When no specific treatment was available there was perhaps little point in isolating these delicate and rather slow-growing organisms This may account for the fact that to the majority of clinicians "anaerobe" has become synonymous with clostridium, and there is little demand for anaerobic culture except from war wounds or when there are clinical signs of gas-gangrene or tetanus

Now that antibiotics are available for treatment, we can no longer afford to ignore the non-sporing anaerobes which are constantly present in the human intestine, upper respiratory tract, and genital passages, and which can infect, sometimes fatally, when they invade unfamiliar sites It is misleading and improper to report "culture sterile" when no attempt has been made to isolate anaerobes Some of the unexplained results, both successes and failures, of antibiotic treatment are due to the unsuspected presence of these organisms The following case-history is an illustration

A middle-aged man was admitted with a high swinging fever and a history of two similar attacks during the previous few months Before treatment a sample of blood was cultured which yielded a growth of a lactose-fermenting bacillus thought to be *Escherichia coli* When the physician in charge was notified he was surprised, because the patient appeared to have responded well to penicillin and had done so on the two previous occasions The coliform was tested to see if it was unusually sensitive to penicillin, but it was found to be resistant Subcultures from the blood-culture were continued and on the 12th day anaerobic cocci and anaerobic fusiform bacilli were isolated which were sensitive to penicillin The coliform was further investigated and found to be *Citrobacter freundii* which is common in soil and water but is unlikely to be a human pathogen All three organisms had probably entered the blood-stream from a paracolic abscess which was later opened and drained Unfortunately the antibiotic treatment given to cover the operation prevented their isolation from the pus

Non-sporing anaerobes, particularly gram-negative bacilli, cannot always be seen in the stained films of specimens which subsequently yield a heavy growth Liquid cultures are unsatisfactory because these organisms are easily outgrown, therefore routine primary culture on blood agar in an anaerobic jar is essential If, for reasons of economy, only one plate culture can be made, an anaerobic one is to be preferred because strict aerobes are extremely rare

Summary

Routine diagnostic cultures made in air and anaerobically show that infection with anaerobes is common

Often the organisms that are important clinically can be shown only on anaerobic culture

I should like to thank Dr J C Hawksley for permission to publish the case-history, Prof Wilson Smith for his encouragement, and all those who have worked in my laboratory during the past six years, particularly Mr R A Bono and Mr L R Jeffries, the results in this paper are largely their work

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THYROID FUNCTION IN PATIENTS WITH MAMMARY CANCER *

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SEVERAL reports suggest an association between the thyroid gland and cancer, especially of the breast

Beatson (1896) thought that the administration of thyroid extract as well as removal of the ovaries might be of value in the treatment of metastatic carcinoma of the breast, and the first patient in his original series was treated with benefit by both methods

More recently others (Stocks 1924) have found evidence of a positive correlation between goitre on the one hand and carcinoma (particularly of the stomach and other parts of the alimentary tract) on the other In a full review of the subject Spencer (1954) confirmed these findings and quoted animal work which also suggested a relation between the thyroid gland and cancer In experiments with carcinogenic agents and with tumour transplantation, thyroxine was found to inhibit the growth of cancer and thiouracil to potentiate it

Sommers (1955) reported histological evidence of thyroid atrophy in patients with advanced carcinoma of the breast Loeser (1954) believed that there was a connection between hypothyroidism and cancer of the female breast and genital tract He advocated the use of thyroid extract as a prophylactic measure against recurrence of cancer and cited 18 patients of his own, treated in this way, who had responded well Lemon (1955, 1957) discussed the use of thyroid and prednisone together in the treatment of metastatic breast cancer He claimed that this combination produced better results than prednisone alone and suggested that the two hormones acted synergically

Our interest in this subject was aroused by a chance observation of our own While investigating patients about to undergo hypophysectomy for carcinoma of the breast, we noticed that some of them had abnormally low thyroid function Closer inspection of the data showed that most of these patients with low thyroid function had bloodborne metastases, whereas most of those with normal function had local disease only

Investigation

67 patients were studied They were divided into two groups on the basis of a full clinical examination and radiography of the chest and skeleton The first group (local disease only) had a tumour confined to the breast, chest wall, or local (axillary or supraclavicular) lymph-glands The second (bloodborne metastases) had distant spread of the disease The ages of the patients were similar in the two groups No patient had received any hormonal therapy

Methods

Thyroid function was estimated in three ways after the *administration of 25 microcuries of radio-iodine* (^{131}I) by mouth

1 The *neck uptake* was measured after four, twenty-four, and forty-eight hours The patient sat midway between two Geiger-Muller tubes, one on each side of the neck, and the count was made during a period of one minute The total dose administered was counted similarly, and the neck count was expressed as a percentage of this

2 The *urinary excretion* was measured with a ring counter in the specimens passed during the periods up to eight, eight to twenty-four, and twenty-four to forty-eight hours after the administration of ^{131}I The T index (Fraser et al 1953) was calculated for each patient

3 The *protein-bound iodine* was measured in a sample of venous blood, withdrawn after forty-eight hours The protein contained in 5 ml of plasma was precipitated and washed with an excess of 10% trichloracetic acid, and then resuspended in 2 0 N sodium hydroxide It was placed in a scintillation counter and counted for about an hour

For several reasons the patients were not all studied by each of the three methods There were, however, no obvious factors which invalidated the random selection of the patients in the two groups

Results

Neck uptake (fig 1)—The maximum uptake found at any of the three times is shown The mean value in group II (bloodborne metastases) is significantly lower than that in group I (local disease only)

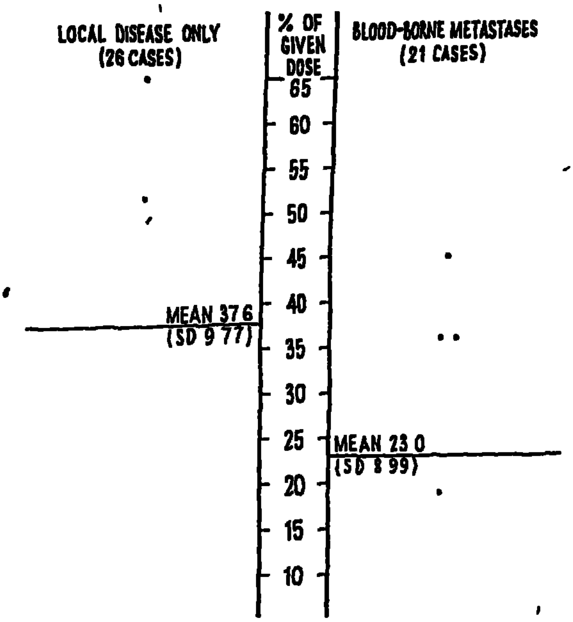

Fig 1—Neck uptake of ^{131}I in patients with carcinoma of the breast Figures represent maximum uptake found within 48 hours of administration Statistical analysis: t(45 D F)=5 3 $P<0 001$

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* Paper read to the Surgical Research Society, November, 1957

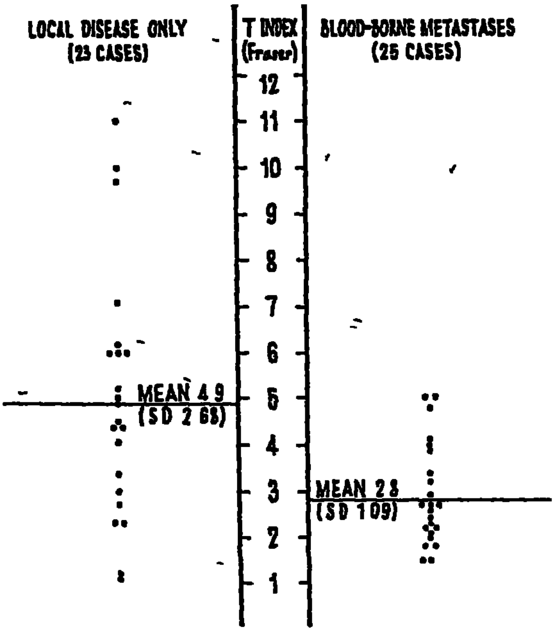

Fig 2—Urinary excretion of ^{131}I in patients with carcinoma of the breast. Statistical analysis t(46 D F)=3·61 P<0·001

Urinary excretion (fig 2) —The mean in group II is similarly lower than that in group I

Serum protein-bound iodine (fig 3) —The mean for group II is again lower than that for group I, but the difference is not significant The method, however, is not very accurate, since in many cases the count obtained was only slightly higher than that of the background.

In many patients, particularly those with bloodborne metastases, the results of the tests were consistent with frank myxœdema, but there were no clinical signs of depressed thyroid function

Because of the possible dangers of radioactive substances we did not study a series of normal euthyroid subjects, but the results in group I (local disease) agree closely with those obtained in normal subjects by other workers (Fraser et al. 1953, Goodwin et al 1951)

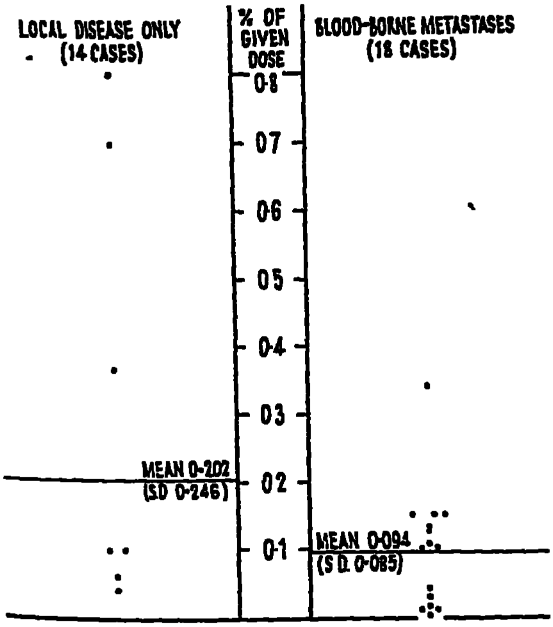

Fig 3—Serum-protein-bound ^{131}I 48 hours after administration of ^{131}I in patients with carcinoma of the breast Statistical analysis: t(30 D F)=1·57 0·1>P>0·05

Discussion

It is clear from our findings that reduced thyroid activity and widespread breast cancer are associated, while normal thyroid function is found in local disease, no matter how far advanced The important question to ask is "Which comes first?" Do bloodborne metastases depress thyroid activity, or does reduced thyroid function favour the distant spread of malignancy? These questions cannot yet be answered, but there are several points in favour of each possibility

Widespread cancer might depress thyroid function in one of two ways

1 Metastases in the pituitary or in the thyroid or in both might destroy functioning tissue Metastases are common in these glands, but they are usually small and do not affect other aspects of pituitary function, indeed, Sommers (1955) has reported hyperplasia of the ovary and the adrenal cortex in patients with metastatic carcinoma of the breast

2 Cachexia and toxæmia might depress pituitary function We think this unlikely, since many of those with locally advanced disease (group I) were more toxic and cachetic than those in the metastatic group (group II)

Further direct evidence could be obtained by studying thyroid function in patients with bloodborne metastases from *other* types of cancer A preliminary study shows that function was normal in 5 such patients whom we tested This suggests, at the moment, that widespread metastases do not of themselves depress thyroid function

The other possibility is that depressed thyroid function might favour the development of distant metastases In support of this are the correlation between reduced thyroid function and a high death-rate from cancer, and the effects of thyroxine and of thiouracil on the behaviour of cancer in laboratory animals Further evidence could be obtained by giving thyroid extract prophylactically to patients who have had primary treatment for uncomplicated breast cancer One of us (A R L) is at present conducting a controlled clinical trial along these lines Two groups of 80 patients who have had primary mastectomy and radiotherapy have been observed for two years One group has had thyroid extract and the other no additional treatment The incidence of recurrence (both local and metastatic) is about 15% in each group A larger series must be followed for a longer period before any conclusion can be drawn

Summary

Thyroid function was studied in patients with carcinoma of the breast by measuring the neck uptake, urinary excretion, and protein-bound fraction of ^{131}I Function was significantly lower in those who had bloodborne metastases than in those who had local or locally advanced disease

We wish to thank Prof G M Bull for the use of the counting apparatus in his department, the nurses in the Royal Victoria Hospital and Northern Ireland Radiotherapy Centre for their help in collecting specimens, Mr G A Smith and Mr R. G Wood for the diagrams, and Miss P Black for typing the script

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DIFFUSE PULMONARY EMPHYSEMA AND PAPILLŒDEMA

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PAPILLŒDEMA, as a complication of gross pulmonary emphysema, was first noted by Cameron (1933) 24 other cases have since been recorded (Loman and Dameshek 1945, Meadows 1947, Beaumont and Hearn 1948, Simpson 1948, 1954, Carter and Fuller 1951, McCann 1951, Mithoefer 1952, Westlake and Kaye 1954, Rossini and Lugaresi 1955, Laterza and Valassi 1956, Seiker and Hickham 1956, Austen et al 1957, Conn et al 1957)

Case-report

A *man, aged 36, had for many years had* recurrent attacks of severe bronchitis associated with increasing dyspnœa of effort Originally a miner, he had been forced by his illness to take progressively lighter work With the passage of the years, the bouts of bronchitis had become more incapacitating For twelve months before admission to hospital, he was troubled by recurrent attacks of severe frontal headache aggravated by coughing and bending For six months he had noted failing vision so that even with a bright light he had difficulty in reading a paper He was admitted to the chest unit, Walker Gate Hospital, on Aug 24, 1957, with a severe degree of right heart failure Throughout his stay in hospital his blood-pressure varied between 110/70 and 120/70 mm Hg There was obvious finger clubbing and central cyanosis The heart-sounds were faint but normal The chest was barrel-shaped and fixed in practically full inspiration There were scattered rhonchi throughout most areas of both lungs and persistent medium coarse moist sounds at both bases There was gross bilateral papillœdema with numerous flame-shaped hæmorrhages, especially close to the swollen optic discs The appearances were more striking on the right side There was myoclonic twitching of the facial muscles while the patient was asleep The Wassermann reaction was negative

On Aug 24 digoxin, intramuscular aminophylline, and intermittent oxygen therapy were started He was also given chloramphenicol to combat any respiratory infection One dose (2 0 ml) of mersalyl was given on admission Next day aminometradine 200 mg three times a day was started, to alternate with acetazolamide 250 mg three times a day The latter was rapidly increased to 1 25 g a day, he was finally stabilised by Aug 28 on acetazolamide 250 mg twice a day, alternating with aminometradine 200 mg twice a day A salt-free diet was started and the fluid intake was restricted to two pints a day An electrocardiogram (E C G), forty-eight hours after admission, showed a severe right ventricular strain pattern with right ventricular hypertrophy On Aug 26 the hæmoglobin was 13 9 g per 100 ml , and the packed cell volume 49%, the red and white blood-cells appeared normal On Aug 27 the plasma-alkali-reserve was 62 vols CO_2 % (28 0 mEq of bicarbonate per litre) A radiograph of his chest on Aug 29 showed the radiographic changes associated with emphysema and a heart of normal shape and size The skull was radiographed the same day and appeared normal

A week after admission, in spite of very rapid improvement in his heart-failure, the patient still had gross papillœdema and complained bitterly of his headache At lumbar puncture, the cerebrospinal fluid (C S F) was at a pressure of 210 mm , with a normal Queckenstedt test There was no pleocytosis, the chloride content was 715 mg , sugar 64 mg , and the protein 40 mg per 100 ml As the headaches remained very troublesome and the papillœdema unchanged, in the absence of obvious clinical hypercapnia, it was decided to carry out a ventriculogram This was completely normal

On Sept 16 the plasma-alkali-reserve was 56 7 vols (25 3 mEq), serum-sodium 143 mEq , serum-potassium 4 3 mEq , and serum-chloride 105 mEq per litre On Sept 19 an E C G showed some improvement in the right ventricular strain pattern On Sept 23, though there was no clinical evidence of heart-failure, the arm-to-tongue circulation-time (using calcium gluconate) was 16 seconds (average of three readings)

On Sept 27 the CO_2 spirogram showed a moderate mixing defect The expiratory flow-rate was considerably reduced, with a vital capacity of less than 2 litres The alveolar CO_2 content was not above normal limits The pH of the whole blood was 7 37, with an arterial plasma-CO_2 of 56 8 vols %, equivalent to an arterial CO_2 tension of 43 mm Hg The oxygen saturation at rest was 91% This picture suggested a ventilatory perfusion defect due to emphysema The patient was no longer orthopnœic, though he was still very breathless on effort, his exercise-tolerance being limited to twenty yards on the flat His papillœdema had improved very considerably, and there were now no hæmorrhages Though he still had headaches, they were less frequent and less severe

At lumbar puncture the C S F pressure was 195 mm , with no pleocytosis and normal chemical findings There was no clinical evidence of heart-failure, and the venous pressure in the antecubital vein at the level of the right auricle was 7 7 cm (normal 4 to 8 cm (Friedfeld and Fishberg 1934)) of saline The patient was finally allowed home on digoxin 0 25 mg twice a day, aminometradine 200 mg twice a day alternating with acetazolamide 250 mg twice a day, no added salt with his meals, and fluid intake restricted to two pints a day Since discharge his breathing has not improved further, and headaches continue to be intermittently troublesome The papillœdema has not recurred

Discussion

Although papillœdema may be associated with hypercapnia (Simpson 1948, Mithoefer 1952, Westlake and Kaye 1954), it can apparently persist in its absence, as in the above case This absence of hypercapnia in the presence of persistent gross papillœdema, severe headache, and altered consciousness may make it difficult to exclude cerebral tumour without special investigations There is no doubt that both hypercapnia and heart-failure will produce a considerable rise in the cerebrospinal-fluid pressure, but in heart-failure this is not associated with papillœdema (Friedfeld and Fishberg 1934)

Acetazolamide ('Diamox') will produce a useful reduction in the bicarbonate level of the plasma, though the process is self-limiting When it is given in hypercapnia, a respiratory acidosis tends to be converted to a metabolic acidosis (Heiskell et al 1954, Bell 1955, Zuniga-Caro and Orrego-Puelma 1957) *It must not* be used in the presence of hepatic insufficiency, because it interferes with the excretion of ammonium ions (Van der Straeten and Verheulen 1956)

In this patient the plasma-bicarbonate fell from 28 8 mEq per litre to 25 3 mEq Some of the change may well have been due to relief of the heart-failure, producing improved respiratory function Aminometradine produces a predominantly chloride ion loss in the urine, and therefore compensates for the metabolic acidosis previously produced by the acetazolamide

Summary

A case is described of diffuse pulmonary emphysema with papillœdema and heart-failure

Papillœdema may be associated with hypercapnia and a rise in the cerebrospinal-fluid pressure, but it can persist for some time in the absence of both Difficulties may arise in distinguishing the condition from cerebral tumour because of the persistence of the papillœdema and severe headache after the heart-failure and the hypercapnia have been relieved

Continued alternating use of acetazolamide and aminometradine is a possible means of partially relieving the respiratory acidosis.

I am indebted to Mr L P Lassman for the ventriculogram, and to Dr L Feinmann for the pulmonary function tests.

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Preliminary Communication

EFFECT OF RESERPINE ON VASOCONSTRICTION CAUSED BY SYMPATHOMIMETIC AMINES

NORADRENALINE was shown by Schmiterlow[1] to be present in extracts of arteries, and recently we observed that when rabbits and dogs were treated with reserpine this noradrenaline was no longer to be found.[2] Nicotine (or acetylcholine in the presence of atropine) injected into the fluid perfusing a rabbit's ear causes vasoconstriction, and we also observed that this vasoconstrictor effect was absent when the ear was taken from a rabbit which had been treated with reserpine. We concluded that nicotine caused vasoconstriction by releasing noradrenaline from the artery wall. Carlsson et al[3] saw that tyramine failed to cause the usual increase of blood-pressure in cats treated with reserpine. We have now confirmed this, using the spinal preparation, and have also observed that tyramine fails to cause contraction of the nictitating membrane of the cat treated with reserpine. We have also found that tyramine, which causes vasoconstriction of the perfused hindleg of the dog, fails to do so if the dog is treated with reserpine. If, however, noradrenaline is infused into the blood during 20–30 minutes, then (after the infusion has stopped and its constrictor effect has disappeared) tyramine causes constriction.

Further, we have observed that the constrictor effect of tyramine in the perfused rabbit ear is greatly reduced when the rabbit has been treated with reserpine. We have therefore reached the provisional conclusion that tyramine acts, on the blood-pressure, on perfused vessels, and on the nictitating membrane by liberating noradrenaline from the store in the artery walls or from a store which is probably present in the nictitating membrane.

We have found that ephedrine and amphetamine have little pressor action in the spinal cat treated with reserpine and they fail to cause contraction of the nictitating membrane. Their constrictor action in the perfused rabbit ear is greatly reduced when the rabbit is treated with reserpine.

Hence nicotine, acetylcholine, tyramine, ephedrine and amphetamine form a group whose vasoconstrictor action is greatly reduced or absent in the vessels of an animal treated with reserpine. We know that such vessels have lost most or all of the noradrenaline which is ordinarily present.

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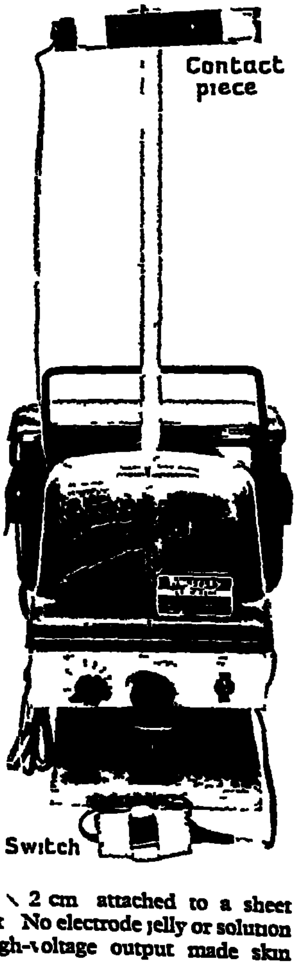
New Inventions

AN ELECTRICAL DEVICE FOR DECONDITIONING

IN the course of attempts to treat a case of spasmodic torticollis apparatus was required which would deliver an electric shock to the patient whenever his head was rotated by the pathological movement. After only partially successful attempts with an electronic stimulator it was decided to modify an "electric fence" of the type used in agriculture.



The machine, made by Wolseley Engineering Ltd., has certain advantages, it is battery-operated by a long-life 6V accumulator, it is self-starting when the primary circuit is closed, it is fairly light and portable, and it is safe for continuous operation because its safety does not depend on the integrity of capacitors.

Briefly, the instrument consists of a transformer. When the primary is closed with a 6V battery in series, an induced shock is delivered at the secondary connections, and the transformer core, acting as a simple electromagnet, initiates the contact breaker to start repetitive cycles.

The present patient, lying down, had a gravity-operated mercury switch strapped by elastic to his head. The switch was oriented so that the primary circuit was closed when his head rotated 30–40° to the right. The secondary circuit was led to a contact piece, on the left arm, which consisted of 2 brass plates 2 × 2 cm attached to a sheet of 'Paxolin', about 40 cm apart. No electrode jelly or solution was required, because the high-voltage output made skin resistance an unimportant factor.

The machine had to be modified because the shock was much too strong for the present purpose. Ten layers were stripped off the secondary winding. This was tedious, and, in the light of other modifications, was probably quite unnecessary, because a potentiometer of lower resistance across the secondary would have served. When this had been done, the shock was still far too intense, and two potentiometers were introduced, one in series with the primary, and one across the secondary in parallel. The potentiometer in the primary circuit was of 500 ohms and acted both to reduce the secondary output and as a speed control The repetition-rate increases with a fall in primary voltage The potentiometer in the secondary circuit was of 50,000 ohms and provided a range of stimulus intensity which was quite reasonable in the present circumstances

The case in which the machine was tried was exceptionally severe, but three weeks' use of the machine produced improvement The equipment is described because it may be useful to others using deconditioning therapy It may prove to be a silent substitute for the electric bell in enuresis alarms The photograph shows the complete apparatus

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Reviews of Books

Chronic Bronchitis, Emphysema, and Cor Pulmonale

C H STUART-HARRIS, M D , F R C P , Sir George Franklin professor of medicine University of Sheffield, T HANLEY, M D , M R C P , lecturer in medicine, University of Sheffield Bristol John Wright 1957 Pp 252 42s

Recent Trends in Chronic Bronchitis

Editor NEVILLE C OSWALD, M D , F R C P , physician, St Bartholomew's and Brompton Hospitals, London London Lloyd-Luke 1958 Pp 191 30s

THESE books come from centres which in recent years have made notable contributions to the literature on chronic bronchitis The views they express are therefore the fruits of broad experience and every aspect of the subject is covered thoroughly

The challenge of chronic bronchitis has been met by workers in many specialties, and sections are devoted to contributions from pathology, applied bacteriology, radiology, cardiology, and respiratory physiology The chapter on pathology by Dr Lynne Reid in Dr Oswald's book is outstanding, and a critical analysis by Professor Stuart-Harris and Dr Hanley of current theories about the pathogenesis of cor pulmonale is particularly stimulating For some time interest has been focused on the relationship between social and environmental factors, such as cigarette smoking and atmospheric pollution, and chronic bronchitis, and the relevant field work and epidemiological studies are presented and discussed Dr Oswald's book also contains a chapter on chronic bronchitis in general practice Both works are first-class expositions of the current investigative approach to chronic bronchitis and its clinical management

Comprehensive accounts of this kind will not, of course, appeal to everyone Despite the intensive effort put into research on chronic bronchitis, the yield of important discoveries has so far been scanty, and readers who seek information only about advances of clinical significance may prefer to get it in shorter form And readers specially interested in chest disease may also find the going heavy since they will already be familiar with the gist of most of the work discussed But both books can be strongly recommended as authoritative appraisals of the contributions from many specialties—pathology, bacteriology, radiology, epidemiology, cardiology, and respiratory physiology—to the fight against chronic bronchitis

Endocrine Aspects of Breast Cancer

Editor ALASTAIR R CURRIE, B SC , M B , F R C P E , senior lecturer in pathology, University of Glasgow Edinburgh and London E & S Livingstone 1958 Pp 340 37s 6d

EVEN when a particular form of cancer is considered from what seems a limited aspect, the many methods appropriate to its investigation may occasion not only interest but bewilderment Great credit is therefore due to the organisers of the recent Glasgow conference on endocrine aspects of breast cancer for an attempt to integrate current thought on this subject The proceedings, published with great dexterity within six months of the conference, record the activities of many research centres throughout the world They are brilliantly edited and summarised to give a concise picture of what is going on

The material has been grouped under four main headings—clinical and pathological aspects of hormonal sensitivity, hormone studies, and experimental pathology The results of adrenalectomy and of pituitary irradiation and ablation in breast cancer are described in detail, and the section on pathology includes a number of interesting reports correlating the histological appearances of the breast, gonads, adrenals, and hypophysis Hormonal studies include important contributions on the assay of pituitary factors and urinary œstrogens, and the experimental section records recent work in animals The book ends with a discriminating summary, which is a well-balanced and easily absorbed account of the whole subject Those concerned in the treatment of breast cancer and in cancer research have good reason to thank Dr Currie and those who helped him to prepare so up-to-date a book

Roentgen Diagnosis of Abdominal Tumours in Childhood

CHARLES M NICE, Jr , M D , PH D , ALEXANDER R MARGULIS, M D , LEO G RIGLER, M D , department of radiology, University of Minnesota Medical School Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 75 30s

THE authors emphasise the value of collecting all possible information about an abdominal mass before planning treatment and considering diagnostic laparotomy, and they believe that radiology has much to offer The careful interpretation of plain films and observation of the displacements of surrounding organs is shown to yield valuable information about the origin and nature of many tumours

The book is intended for radiologists, pædiatricians, and surgeons There are no technical details of special radiographic methods, such as presacral insufflation, though their scope is discussed The tumours are classified on a regional basis, and in the discussion of the different types of mass the clinical and pathological comments seem to be too brief to be of much value to clinicians, though they may serve as useful reminders to radiologists The illustrations are adequate and well chosen to bring out particular points There are many references to the opinions of other authorities, and the authors' personal experience is evident in a sound though rather long exposition

The book is helpful in reconsidering the uses of radiology in the investigation of abdominal masses in children, and it makes no exaggerated claims

Parasitology in Relation to Clinical Medicine

K D CHATTERJEE, M D , physician, R G Kar Medical College Hospitals, Belgachia, Calcutta Published by the author, 6, Amrita Banerjee Road, Kalighat, Calcutta 26, India 1957 Pp 185 Rs 12 50

THIS book provides, the author explains, the basic facts contained in his larger work, *Human Parasites and Parasitic Diseases*, and it is designed for medical students and others who want a handy reference book The 76 illustrations add greatly to its value and there are 6 good coloured plates

Some readers will not agree that parasitism can be adequately defined as " the relation that exists between parasites and hosts ", that mutualism, symbiosis, and commensalism are subsections of parasitism, or that the word infection refers to internal parasites and infestation to external parasites But these and some other debatable statements in the general introduction do not detract from the value of the rest of the book, which is a well-arranged compendium of the basic facts of human protozoology and helminthology The emphasis is on biology, pathology, clinical signs, and diagnosis, for amplification of the brief notes on prophylaxis and treatment the reader must turn to larger works

THE LANCET

LONDON 29 MARCH 1958

Hypothermia

HYPOTHERMIA was introduced as an aid to surgery some eight years ago, and its value has proved to be greatest in cardiovascular and cerebral operations. There are two main methods of inducing hypothermia—surface cooling and blood-stream cooling—and both are used in conjunction with general anæsthesia.

Surface cooling was first undertaken experimentally by SIMPSON and HERRING in 1905,[1] then in man by TEMPLE FAY[2] in treating carcinoma, and subsequently in Toronto by BIGELOW et al.,[3] who pioneered its present uses. The methods of cooling include packing the body in ice, immersion in cold water, applying a cooling blanket, and directing a stream of cold air over the surface of the body. These are by far the most widely used methods, and although perhaps rather slow have proved satisfactory.

Blood-stream cooling was introduced by BOEREMA[4] in Holland and DELORME[5] in this country, who made an arteriovenous shunt via an extracorporeal cooling coil. This was improved by ROSS,[6] who made a venovenous shunt by sucking the blood out of the superior vena cava through a catheter, pumping it through a cooling coil, and returning it to the inferior vena cava. Blood-stream cooling, which has been very successful in the hands of BROCK and ROSS,[7] has the advantages of speed of induction and the choice of not using it until the chest has been opened and the necessity for it determined.

The main complication of hypothermia is ventricular fibrillation, but the incidence of this has been greatly reduced since it was realised that a temperature of 28–30°C is satisfactory for most purposes. Cardiac arrhythmia may be avoided by preventing the temperature falling below this level, and by ensuring that there are no temperature gradients between different parts of the body, and that the temperature falls steadily without sudden changes. The long action and delayed inactivation of anæsthetic drugs, notably the barbiturates and curare, may cause complications during re-warming unless great care is taken. Otherwise surprisingly few disadvantages have manifested themselves. The experimental work of SARAJAS et al[8] on dogs raises one disturbing point. They showed that dogs which were subjected to hypothermia and then killed some time after recovery showed considerable pathological changes in the myocardium, in the form of localised fibrinous pericarditis and multiple small areas of myocardial necrosis. These necrotic areas healed rapidly and were replaced by scar tissue, and were not fatal. SARAJAS et al suggested that these numerous small infarctions might cause cardiac arrhythmias if they developed in the conducting tissue of the heart. No evidence has yet been reported of similar findings in man, but clarification of this point is urgently needed. On the other hand MCMILLAN et al[9] showed that the work potential of the hypothermic dog heart was not diminished and that there was no evidence of failure in the clinical range of 28–37°C.

The clinical use of hypothermia has been very widely reported in Canada, where it originated, and in this and other countries—notably the United States.[10,11] In cardiac surgery it enables operations to be carried out on the heart with the circulation arrested for up to 8 minutes in comparative safety, and in many cases the circulation has been arrested for as long as 12–14 minutes. With hypothermia it has proved possible to repair atrial septal defects of the secundum type,[12] and to make an open direct-vision approach to lesions of the pulmonary and aortic valves and in infundibular pulmonary stenosis. Hypothermia has been used also, though not so successfully, in some cases of ventricular septal defect. In vascular surgery it is used mainly for resecting aneurysms where the aorta needs to be occluded longer than the 20 minutes which is normally the longest time compatible with survival of the spinal cord.[13] Hypothermia can increase this time threefold. (For operations on the aorta distal to the origin of the renal vessels there is no need for hypothermia.) Despite hypothermia paraplegia due to thrombosis of the spinal arteries develops occasionally in cases where the blood-flow is arrested during aortic occlusion—particularly occlusion of the lower thoracic aorta. Hypothermia is also used in neurosurgery where the internal carotid vessels have to be occluded either in the neck in order to remove a lesion in the artery[14] or inside the skull in order to deal with a ruptured aneurysm.[15] The shrinkage of the brain produced by hypothermia and the associated hypotension may be useful also in other neurosurgical operations.

The experimental use of deep hypothermia down to temperatures around 0°C has been reported by ANDJUS[16] and SMITH[17] in small animals and by LEWIS[18] in dogs. At these temperatures respiration is arrested, and then the heart slows and finally is arrested somewhere below 10°C. The technique of inducing deep hypothermia in this way bears little relation to clinical methods, but in rats and hamsters recovery-rates of up to 75% have been obtained. In larger animals such as dogs results are not yet so good, and it remains to be seen whether this technique can be improved sufficiently for it to be applied eventually in cardiac surgery. Owing to the virtually complete cessation of metabolic activity at these low temperatures, the method offers the possibility of almost unlimited time to operate on the arrested heart and on the brain.

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It was to be expected that, with the development of machines for extracorporeal circulation, heart-lung bypass and hypothermia should be combined in order to gain the advantages of each method Results so far show that a low-flow heart-lung bypass of about 30 ml per kg body-weight per min combined with hypothermia to 28°C may be successful[19, 20] The induction of hypothermia by an extracorporeal circulation is simple, and the design of the bypass machine may be simplified because of the reduced demands on it Reduction of the body-temperature below 20°C by surface cooling is very difficult, but with a bypass much lower temperatures can be reached[21] Use of the bypass pump is also a major factor in successful re-warming, and, if no serious pathological changes are found to be caused by these temperatures, the combination of hypothermia and a low-flow bypass at temperatures around 10°C may be the best of all the methods discussed here Possibly this will be the most satisfactory method of cardiac arrest for more than an hour—which will be necessary in order to tackle the remaining unsolved problems of congenital and acquired heart-disease About $1^1/_2$ hours is the limit of heart-lung bypass under present conditions Another approach, which is also still experimental, consists in localised cooling of individual organs, such as the brain[7, 22] It must be emphasised that these approaches are purely experimental, and if ever they can be applied clinically it will not be for a long time

Of the existing techniques of hypothermia and heart-lung bypass it is too early to suggest which is the best for a given case, since the choice depends on the skill and experience of the particular team

Cardiac Fibrillation

ATRIAL fibrillation is one of the commonest arrhythmias Its most usual causes are mitral-valve disease, thyrotoxicosis, ischæmic heart-disease, and constrictive pericarditis, occasionally it arises as an isolated abnormality[23] The mechanism of fibrillation has been extensively studied, with contributions first by SIR THOMAS LEWIS,[24] later by PRINZMETAL et al,[25, 26] and most recently by BURN et al[27-31] LEWIS[24] believed that atrial fibrillation was due to a circus movement which pursued an irregular path through the atria round the venæ cavæ, sending off irregular daughter waves to the remainder of the atrial mass This view was widely accepted until PRINZMETAL et al,[25] using techniques of high-speed cinematography that had not been developed in LEWIS' time, were able to show the atrial contraction wave in minute detail These workers produced arrhythmias by damaging the atrium with aconitine, freezing, or electrical stimulation The cinematographic studies revealed two features—minute irregular contractions (M waves) continuously present, and large rhythmic contractions (L waves) The M waves could not be seen with the naked eye, but the L waves formed the visible contractions in the fibrillating atrium They did not pursue a circus movement, and no daughter waves were seen. Simultaneous oscillographic observations of the intrinsic deflection produced at various points in the atria confirmed the absence of circus movement and showed that the arrhythmia was due to discharge from a single ectopic focus Graded damage to atrial muscle was found to produce, in succession, ectopic beats, atrial tachycardia, atrial flutter, and finally fibrillation, the type of arrhythmia depending on the speed of discharge from the focus When the rate of discharge from the focus exceeded a critical level, flutter gave way to fibrillation

This unitary concept of atrial arrhythmias has now been generally accepted, but there is much to be said for maintaining a clinical differentiation These various arrythmias have important practical differences, fibrillation causes a totally irregular ventricular rhythm, while flutter is associated with a regular ventricular action with atrioventricular block—usually 2 or 3 to 1 Flutter can sometimes be distinguished clinically from atrial tachycardia (with 1 to 1 atrioventricular response) by noting pulsation in the jugular venous pulse at double or treble the ventricular rate Carotid-sinus pressure may abolish atrial tachycardia but merely increases the atrioventricular block in flutter, whereas it *has no effect* on fibrillation There are also important cardiographic differences, the characteristic "saw-tooth" flutter waves being usually well seen in standard lead II, in contrast to the abnormal (often inverted) P wave with 1 to 1 atrioventricular response in atrial tachycardia, and the totally irregular F waves of fibrillation But in some cases, as might be expected, the F waves of fibrillation closely resemble those of flutter, when the arrhythmia is sometimes termed "flutter-fibrillation" The implications of these arrhythmias also differ Atrial tachycardia arises commonly in patients with otherwise normal hearts, and may be associated with the accelerated conduction (Wolff-Parkinson-White syndrome[32]) Flutter develops sometimes, and fibrillation commonly, in rheumatic heart-disease, in which atrial tachycardia is less common

The local physicochemical abnormalities in the atria which induce fibrillation have been investigated by BURN et al[27-31] Atrial fibrillation can be produced in the heart-lung preparation of the dog,[27] and in the isolated rabbit heart,[30] by electrical stimulation at frequencies of 500-800 per minute in the presence of acetylcholine BURN et al[28] suggested that acetylcholine maintained fibrillation by its excitatory action on atrial tissue, which is normally not evident because of its overriding inhibitory action on the pacemaker If

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the pacemaker is bypassed by rapid electrical stimulation, the excitatory action is revealed and fibrillation results Burn et al [29] showed that infusion of potassium chloride caused fibrillation to be supplanted by sinus rhythm, and thought that an increase in membrane permeability to potassium ions with increased loss of potassium was probably concerned in the production of fibrillation Acetylcholine may directly change the tissue stimulated so that it becomes an ectopic focus, but its action in maintaining fibrillation after stimulation has ceased may not necessarily be due to any alteration at the point of stimulation Failure to restore normal rhythm by tying off with a ligature the stimulated portion of atrium suggested that this was not acting as an ectopic focus Holland and Burn [8] claimed that, when the atria contract, sodium enters the cell, and potassium leaves the cells Restoration of the potassium within the cells is less likely if the external concentration of potassium is low, and this may be why the low potassium concentration favours fibrillation Harris and Hutter [33] showed that the cell membrane is much more permeable to potassium in the presence of high concentrations of acetylcholine, which greatly shortens the refractory period [34] When the external concentration of potassium is raised, fibrillation ceases [29] Thus the experimental production of fibrillation depends on three factors a low concentration of potassium, a high concentration of acetylcholine, and electrical stimulation at a high rate Fibrillation having been produced, it will continue after stimulation has ceased if the acetylcholine concentration remains high and the potassium concentration low Quinidine, which increases the duration of the action potential, arrests fibrillation, possibly owing to a decrease in permeability of the cell membrane to potassium [35 36] Prinzmetal et al [26] believe that quinidine abolishes fibrillation either by lengthening the refractory period or by depressing the ectopic focus The work of Burn and his colleagues suggests that the former may be the primary mechanism.

Ventricular fibrillation is often a terminal event in severe heart-disease, but, since the advent of cardiac surgery, it has proved reversible In animals ventricular fibrillation constantly develops when the body temperature falls below 20°C,[37] and is often irreversible The same hazard exists at higher temperatures during hypothermia for cardiac surgery, such as the closure of atrial septal defects,[38] when it can sometimes be reversed by rewarming and by the electrical defibrillator Cookson et al [39] suggested that sudden release of caval clamps flooded the heart with a high concentration of adrenaline released from the adrenal glands by anoxia, and dammed back in the caval blood during clamping But Neil et al.[40] found that the circulatory occlusion produced by clamping the cavæ caused considerable metabolic acidosis, which might be related to ventricular fibrillation Lynn et al [41] reported that controlled respiration has a protective action, possibly by maintaining blood-pressure and coronary circulation Swan [42] and Sellick [43] believe that injection of neostigmine into the coronary circulation via the proximal aorta before the heart is opened confers much protection against fibrillation, and Prevedel et al [44] suggested that this effect was due to accumulation of acetylcholine Thus the available evidence suggests that ventricular fibrillation may not be due to the same mechanisms as atrial fibrillation In atrial fibrillation excess of acetylcholine seems to be an important precipitating factor, in contrast to its protective action against ventricular fibrillation

Burn [31] has also studied ventricular fibrillation produced by electrical stimulation He and his colleagues noted that acetylcholine had no action in preventing or inducing ventricular fibrillation in animals After stimulation had ceased, fibrillation would continue if the potassium concentration was reduced, and cease if the potassium concentration was increased When the calcium concentration was also reduced fibrillation did not occur, suggesting that spontaneous fibrillation may be due to a rise in the calcium/potassium ratio, as was suggested by Melrose,[45] rather than to the fall in potassium Perfusion with adenosine triphosphate (A T P) caused reversion to sinus rhythm Since A.T P does not penetrate the cells, this effect cannot be due to metabolic processes within the cell, but it may be due to combination with calcium ions in the cell membrane, causing a fall in calcium concentration Both magnesium and chelating agents such as sodium edetate ('Versene'), which binds calcium ions, also arrested fibrillation [31] In dogs intravenous quinidine sulphate has been shown to give significant protection against ventricular fibrillation [46] Curiously enough, Burn [31] reported that cooling from 37°C to 32°C caused fibrillation to be replaced by sinus rhythm, while rewarming to 37°C again produced fibrillation The confusion about the cause of ventricular fibrillation at low temperatures has been pointed out by Scurr [47] For example, Sealy et al [48] thought that fibrillation following hypercapnœa was due to a high concentration of potassium, while Swan et al [49] regard hypokalæmia as the cause

An obvious difficulty in assessing the cause of fibrillation is that this arrhythmia is the final common path of cardiac failure in hearts damaged by a variety of conditions Whatever the mechanism, it is clear that electrolyte disorder (especially disturbances of calcium-potassium balance), extreme cold, and severe cardiac disease (notably ischæmia) are potent causes It is especially interesting that acetylcholine, which in the animal heart plays so important a part in the maintenance of atrial fibrillation, has no effect on ventricular fibrillation under the same conditions, and in the cooled human heart apparently prevents ventricular fibrillation

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Metabolic Effects of Brain Injury

THE earliest experimental evidence that cerebral injury may produce metabolic disturbances was obtained by CLAUDE BERNARD in a famous experiment in which damage to the floor of the fourth ventricle of rabbits and dogs was followed by hyperglycæmia and glycosuria Equally interesting is his further observation, confirmed by ECKHARD [1] and others, that a unilateral lesion placed more rostrally in the floor of the fourth ventricle may provoke diuresis without hyperglycæmia JUNGMANN and MEYER [2] later found that this diuresis was accompanied by increased excretion of chloride ions WISE [3] has recently demonstrated that bipolar stimulation of the caudal portion of the floor of the fourth ventricle in dogs results in increased excretion of sodium and chloride All these metabolic effects probably result from damage to or irritation of descending fibres which ultimately impinge on the sympathetic outflow from the spinal cord, BERNARD himself showed that hyperglycæmia did not occur when the spinal cord had been cut just above the sympathetic outflow, and section of the splanchnic nerves [1] and denervation of the kidney [4] cause increased excretion of chloride and sodium ions At least the hyperglycæmic effect is independent of the adrenal glands, for it is observed after bilateral adrenalectomy [5]

In an effort to trace the origin of such descending impulses, experimental work has shifted from the medulla to higher levels of the brain The hypothalamus is now known to be particularly concerned with water, electrolyte, and carbohydrate metabolism, and lesions in its various parts may result in hyperglycæmia with glycosuria,[6-8] hypoglycæmia,[9] diabetes insipidus,[6, 10-12] hyperchloræmia with hypochloruria but without polyuria,[7] hyperphagia with obesity,[13, 14] aphagia,[14] and disturbances of the normal secretion of corticotrophin [15, 16] There is evidence too of a "drinking" centre in the dorsal hypothalamus [17] Metabolic effects may also result from stimulation of the brain at levels above the hypothalamus Hoff et al [18] claim that in cats electrical stimulation of foci on the anterior sigmoid gyri of the cerebral cortex results in renal cortical ischæmia, sometimes together with glycosuria In cats and monkeys stimulation of the posterior orbital surface of the frontal lobe, of the hippocampal gyrus, and of the tip of the temporal lobe causes a moderate rise in the blood-sugar level, whereas stimulation of the anterior cingulate gyrus causes a fall [19] These sites belong to the limbic system ("visceral" brain), which is known to send descending connections to the hypothalamus

It is therefore not surprising that in man cerebral injury causes disturbances of metabolism, and four such disturbances—diabetes insipidus, hypothalamic obesity, hyperglycæmia with glycosuria, and respiratory alkalosis—have long been recognised The first three of these are found with lesions which correspond closely to' those producing similar disturbances in laboratory animals The fourth—respiratory alkalosis—arises when over-stimulation of the respiratory centres by irritative lesions in the brain-stem causes hyperventilation with excessive loss of carbon dioxide and consequent alkalosis Evidence has accumulated of other metabolic lesions associated with cerebral injury, and, in particular, two different clinical disturbances of sodium and chloride balance have become well defined ALLOTT in 1939 [20] and subsequently other investigators have reported hypernatræmia and hyperchloræmia with hyponatruria and hypochloruria in association with cerebral vascular accidents, prefrontal leucotomy,[21] head injury,[22] pituitary tumours,[23] and polioencephalitis [24], there is no evidence of renal damage The reverse state—hyponatræmia and hypochloræmia with hypernatruria and hyperchloruria—has been described in patients with cerebrovascular disease, diffuse encephalitis and bulbar poliomyelitis,[25] head injury,[22] and tumours of the posterior thalamus [26] and of the floor of the fourth ventricle [3 25]

As regards the first of these two metabolic disorders, a very similar picture of hypernatræmia with hyponatruria without renal damage may result from other circumstances, such as diabetic coma,[27] gastrointestinal hæmorrhage,[28] and abdominal operation [29], but most of the cases arise after cerebral injury An increased intake of water apparently reduces the hypernatræmia and hyperchloræmia Hypernatræmia may also follow cerebral injury in the unconscious patient when there is water deprivation [22] or undetected diabetes insipidus,[30] or when high-protein diets are taken containing relatively large amounts of sodium chloride but inadequate amounts of water [31]

Many workers have been unwilling to recognise encephalogenic hypernatræmia as a primary entity, ascribing it to one or more of the other causes, or to an unusual metabolic response to a fall in circulating blood-volume.[32] But hypernatræmia and hyponatruria can develop when the patient is on a low-protein and low-sodium diet, and can be clearly distinguished by the history of fluid loss from simple water deprivation, in which, moreover, the urinary concentrations of sodium and chloride are initially high. The condition arises commonly without evidence of a low circulating-blood volume. It differs too from diabetes insipidus in that the urinary specific gravity is usually above 1.020 and the urinary volume is never excessively high and does not exceed the fluid intake, whereas when diabetes insipidus follows head injury the urinary output is high and the specific gravity low.

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That there is excessive tubular reabsorption of sodium and chloride in encephalogenic hypernatræmia is clear,[27] and in one case increased urinary excretion of aldosterone was reported.[24] Even if it be accepted that hyponatruria and hypochloruria result from excessive production of this hormone, three questions remain to be answered: how is excessive aldosterone production stimulated, how does hypernatræmia arise (for increased tubular reabsorption of sodium could not alone bring this about), and how is the site of injury related to the whole condition? It is known that lack of antidiuretic hormone (A.D.H.) provokes aldosterone secretion[33], but A.D.H. excretion in the hypernatræmic state has not yet been estimated, and the clinical evidence against such a mechanism has already been stated. HIGGINS et al.[34] have noted the difficulty of accounting for hypernatræmia and hyperchloræmia unless these ions are transferred from elsewhere in the body, and ALLOTT[24] has recorded a similar difficulty in explaining where the ions go when, during recovery, their plasma-levels fall but they do not appear in the urine. It is known that hypernatræmia with hyponatruria occurs when the orbital surface of the frontal lobes or the hypothalamus are damaged, but the brain has not been exhaustively examined at necropsy. In connecting the frontal lobes with disturbances of sodium and chloride balance, clinical observation is ahead of experimental neurophysiology.

The converse metabolic disturbance—hyponatræmia with hypernatruria—does not appear to result from simple adrenal failure, for no increase of plasma-sodium concentration is brought about by administering deoxycortone or cortisone. These compounds cause retention of sodium, chloride, and water as œdema without return of the plasma concentrations to normal.[22] In one patient who was fully investigated by CORT,[26] the excretion of 17-ketosteroids, 17-hydroxysteroids, and gonadotrophins was normal, as was the fall in eosinophil count after injection of corticotrophin. The experimental evidence suggests that cerebral damage could be the initiating cause of the sodium loss, but the mechanism is not clear.

The incidence of these disturbances of sodium and chloride metabolism after head injury is so high (12% of patients who are unconscious after twelve hours become hypernatræmic and 7% hyponatræmic[22]) as to justify routine estimation of plasma and urinary sodium and chloride on the third day of coma and then at intervals for two weeks. Uncorrected hypernatræmia, possibly because of hyperosmolarity, and uncorrected hyponatræmia are associated with a high mortality. Estimating only the urinary sodium or chloride concentration may, in these conditions, be very misleading.[29] These metabolic disturbances support the view that extracellular concentrations of sodium and chloride are controlled by a central mechanism different from that controlling body-water content. It would be interesting to learn how such a central mechanism may exert an effect on the kidneys and on the movements of ions. There is a hint, too, of a pathway from the frontal lobes via the hypothalamus into the brain-stem, which might well repay the exhaustive attention of the neuropathologist in fatal cases.

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Annotations

THE HALIFAX SURVEY

ANYONE who believes that the standards of health, safety, and welfare in British factories are high should read *A Survey in Halifax*,[1] which contains a report by factory inspectors on the 760 factories in this Yorkshire town. Although this account covers only one town there is no reason to believe that the conditions would prove very different in many other industrial towns in Great Britain. In nearly 200 factories the general working environment was unsatisfactory, in over 200, washing facilities, cleanliness, and ventilation were unsatisfactory. A few small factories had no water-carriage system of sanitation, and in 76 the lavatories were outside the main building. A tenth of the factory buildings were dilapidated and no longer weatherproof. Old rented property was often poorly decorated. Many workplaces had poor first-aid arrangements, neglecting elementary principles of cleanliness and of using dressings. These sordid conditions, reminiscent of a previous age and seemingly out of place in a prosperous society now concerned about the threats of good living[2], were not just the lot of a few. They were more often found in the smaller than in the larger factories, but the proportion of manual workers in factories with less than 101 operatives is 38% in Halifax and 35% in Great Britain. In the 760 Halifax factories, which altogether employ 29,000 manual workers, there were 12 full-time nurses (9 State-registered, 3 State-enrolled assistant nurses) and 4 part-time doctors, who served respectively 23 and 21 of the factories. The total hours of employment in industry of all these doctors were not more than 15 a week. Most of their time was given to routine medical examinations, and few observations were made of the environment and of persons actually at work.

In this type of general survey, in which neither workers nor their environment can be studied with scientific precision, it is not possible to elucidate new or suspected hazards or to assess the extent of old ones. Nevertheless, some hazardous processes were seen—for example, work with brick, silica stone, and fireclay, boiler-scaling, and foundry processes. Toxic solvents were widely used—often in small amounts, though this did not necessarily

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1. Industrial Health—A Survey in Halifax. A report by H.M. Factory Inspectorate and Recommendations of the Industrial Health Advisory Committee. H.M. Stationery Office. 1958. Pp. 20. 1s. 6d.
2. Vickers, G. *Lancet*, March 22, 1958, p. 599.

mean that there was no danger to health A few of the larger factories in Britain, and the Slough Industrial Health Service, have their own industrial hygienists who can measure dust and fume concentrations in the atmosphere of workrooms, but the Industrial Health Advisory Committee stresses in this report that there is no means of getting precise information about environmental contaminants in most British factories

Several conclusions may be drawn from this report There are probably many factory occupiers in this country who are not observing simple rules of factory hygiene Although the cost of this neglect in terms of accident, illness, and poor morale cannot be measured, it is only common sense to suggest that these rules should be observed The 300 or so factory inspectors responsible for routine inspections of some 270,000 workplaces[3] (including docks, warehouses, and building sites) cannot do this work on their own But they could get more help with the very small factories from two readily available sources the medical officers of health and their health inspectors, who are responsible for inspecting lavatories in all factories, as well as cleanliness, overcrowding, temperature, ventilation, and drainage of floors in factories without mechanical power, and the 1750 or more appointed factory doctors, who examine young persons and those employed in certain dangerous trades They could spend more time observing factory conditions and advising management where to make improvements

A fully comprehensive industrial medical service presents serious problems of organisation and supply[2] It may be possible to provide every factory with a doctor and a nurse It is much harder to ensure that the health of workers is properly cared for It is doubtful whether the very small undertakings need such services, but there is a need for them in the larger factories In 1949, of the 4800 factories with 250 or more workers, less than half had medical supervision additional to the statutory examinations of young persons[4] There is no reason to believe that there has been much change in nine years Here there is scope for immediate expansion Much of the work would have to be done by general practitioners in the National Health Service The Halifax survey has shown that they should be trained to practise industrial medicine There are enough university departments of social medicine and occupational health to do this with the help of the growing body of experienced industrial medical officers This would help the Factory Department in its big task of raising and maintaining standards of health, safety, and welfare in factories and other types of workplaces—particularly works of engineering construction and building operations It could give a new interest to general practice and, in time, relieve the hospitals of some of their less important routine work

The survey reveals that an industrial hygiene laboratory service is urgently needed Big cities such as Manchester, Birmingham, and Glasgow have no centres to which industrial medical officers and factory inspectors may readily refer for assistance in measuring exposures to contaminants such as dusts, fumes, and ionising radiations

The growing problems in occupational health have been carefully considered by committees of the Government, the Royal College of Physicians, the British Medical Association, and the Trades Union Congress, but progress has been very slow The Halifax survey, which upholds the traditions of the Factory Inspectorate for careful and critical reporting, emphasises again that action to develop occupational health services is long overdue

SMOKING AND RESTLESS YOUNG MEN

It is now generally accepted not only that there is an association between cigarette smoking and lung cancer, but also that cigarette smoking increases liability to lung cancer But some have suggested that people who are constitutionally predisposed to smoking may also be constitutionally predisposed to cancer and that the relation of smoking and lung cancer may thus not be one of cause and effect A report by Heath[1] of differences between smokers and non-smokers is therefore of interest

In order to study adult development the progress of normal college men, selected and examined in the years 1938–42, was checked by interview and questionary Information about smoking habits was among the data collected The material for Heath's study was obtained from the records of 252 of these men whom it had been possible to follow up adequately until 1957 Their ages at that time ranged from 33 to 37

The men were classified according to their smoking habits over the period of observation into non-smokers, moderate smokers, and heavy smokers There were 61 (24%) non-smokers, of whom 51 had never smoked at all, and 10 had smoked only rarely and intermittently before 1947, 95 (38%) moderate smokers, of whom 65 smoked up to 19 cigarettes a day and 30 smoked chiefly a pipe or cigars, and 96 (38%) heavy smokers, all of whom smoked 20 or more cigarettes a day either continuously or for a majority of the observation years

When the histories of the 5 heaviest smokers in the series were compared with the histories of 5 randomly selected non-smokers, temperamental differences between the two groups became apparent The heavy smokers tended to be restless, energetic, impulsive, independent, interesting men, ardent in the pursuit of enterprises which appealed to them, and seeking service during the war with combat units, they were apt to run into marital difficulties The non-smokers were bland, steady, dependable, hard-working, rather uncommunicative family men who tended during the war to gravitate to specialised non-combat units These temperamental differences between smokers and non-smokers were confirmed when categorised personality traits and other distinguishing characteristics were allocated to each member of the series and the results subjected to statistical analysis Other differences were also observed at college non-smokers liked science, smokers the arts, non-smokers tended to choose scientific careers, moderate smokers careers in business or medicine, heavy smokers had few career preferences, but disliked jobs connected with science, and those who indulged more in tobacco tended also to indulge more in alcohol and coffee

A comparison of smoking habits with a wide variety of physiological and medical data gave largely negative results, although the heavier smokers tended to be rapid breathers and have reduced reflexes Over the years heavy smokers tended to lose weight (although initially they had the heartiest appetites), moderate smokers to gain weight, and non-smokers to weigh about the same

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[3] Staffing and Organisation of the Factory Inspectorate Cmd 9879 H M Stationery Office, 1956

[4] Report of a Committee of Enquiry on Industrial Health Services Cmd 8170 H M Stationery Office, 1951

[1] Heath, C W *Arch intern Med* 1958, 101, 377

Heath admits that if a different population were similarly examined it would be unlikely that his findings would be exactly duplicated, but he considers that they indicate that smoking is a habit acquired, not haphazard, but as a consequence of certain personality traits and physiological characteristics It is not difficult to accept that personality type may be at any rate one of the factors determining whether a man becomes a smoker bland, judicious, uncommunicative young men may well be less responsive than their more sociable and dashing fellows to such influences in favour of smoking as example and advertisement, and it also seems likely that addicts with a high degree of emotional tension will smoke most heavily It is much less easy to accept the suggestion that the distinguishing features noted in smokers "may have just as much right to a place in the etiology of disease as the tobacco smoke ingestion itself"—if by disease is meant lung cancer To explain the increase in lung cancer on this basis, it would be necessary to postulate that the personality pattern of the population was altering, and altering in such a way as to make the lungs especially susceptible to cancer—a somewhat dubious proposition Again Heath draws no distinction between the personality of cigarette smokers and pipe smokers, and it is difficult not to be impressed by the observation[2] that cigarette smokers who draw tobacco fumes into their lungs are more liable to lung cancer than pipe smokers, who are much less apt to do so Certainly from a practical point of view it is important to bear in mind the finding[2] that cigarette smokers who give up tobacco reduce their liability to lung cancer, for this suggests that the prospects for restless young men are reasonable if they can be persuaded to abstain

SOURCES OF GASTROINTESTINAL BLEEDING

MAJOR upper-gastrointestinal hæmorrhage originates from chronic or acute peptic ulcers in over 90% of patients seen in London by Avery Jones[3], portal hypertension is responsible in only 3% In contrast, a third of the patients with upper-gastrointestinal hæmorrhage in the Massachusetts General Hospital are bleeding from gastro-œsophageal varices[4], and in Boston gastritis is also a common cause of hæmorrhage[5] Such variations, which are partly determined by differences in alcohol consumption, are important because successful management depends on accurate diagnosis

In patients with peptic ulcer a correct diagnosis is often suggested by the history and physical findings, but such evidence may be either lacking or misleading Similarly, a history and physical stigmata compatible with cirrhosis—particularly splenomegaly or other signs of portal hypertension—constitute a valuable guide, but they are not invariably found in patients with chronic liver disease In addition, the frequent coexistence of peptic ulcer and cirrhosis[6] raises a subtle clinical problem regarding the site of bleeding

When mixed lesions are present precise identification of the bleeding site is especially desirable, and this is possible only by endoscopy or laparotomy Emergency œsophagoscopy can be done successfully in the ward or, like gastroscopy, under anæsthesia before operation. Both techniques are unreliable when bleeding is heavy Acute lesions of the stomach can be shown only by gastroscopy, but for identification of chronic ulcers gastroscopy is apt to be less satisfactory in men (because they bleed most often from duodenal ulcers) than in women Less direct information may be gained by introducing a gastro-œsophageal compression balloon, control of the hæmorrhage being presumptive evidence of œsophageal varices Alternatively, the staining by blood on a string swallowed by the patient[7] may indicate the position of the bleeding site when hæmorrhage is less severe

An emergency barium swallow and meal examination is now generally considered reasonably free from risk and will usually demonstrate varices or a chronic ulcer[8] Portal venography shows varices more accurately[9] and in some centres it can be used as an emergency procedure It has the added advantage of demonstrating preoperatively the patency or otherwise of the portal vein. In patients with acute lesions and negative X-ray findings, a history of salicylate consumption, tests of gastric secretion, or hæmatological investigations can be helpful

Biochemical tests of liver function—especially the degree of bromsulphalein retention[10]—may confirm the presence of liver disease, but do not necessarily indicate portal hypertension McDermott[11] has found the bromsulphalein test unsatisfactory, and advocates estimation of the peripheral-vein ammonia content, an increase suggests the presence of portal collateral veins (which deliver ammonia derived from blood in the intestines direct to the systemic circulation) rather than impaired hepatic metabolism of ammonia[12] McDermott's results support the value of this test, especially as he has devised a qualitative method that eliminates many technical difficulties The procedure is still likely to prove too capricious for occasional use, but it will be valuable where the possibility of hæmorrhage from varices often presents itself

Thus, gastrointestinal hæmorrhage of uncertain cause can be investigated clinically, the approach will depend on the patient, environmental circumstances, and hospital facilities The enlightened integration of medical, radiological, surgical, and biochemical techniques should ensure that few patients with hæmatemesis or melæna or both come to laparotomy (or leave hospital) without its origin having been determined

A NEW CHAIR IN ANÆSTHESIA

A GIFT of £150,000 from the British Oxygen Company has made possible a chair of anæsthesia at the Royal College of Surgeons of England Making known this benefaction last week, Dr Frankis Evans, dean of the Faculty of Anæsthetists, announced that Dr R. F Woolmer, now director of the department of anæsthetics at the college, would be the first professor This is the first chair of anæsthesia in London, and its creation will afford new opportunities for investigation in a department that has rapidly made itself a name for vigour and ingenuity in research

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SIR ALEXANDER RUSSELL, formerly public health commissioner with the Government of India, died on March 22 at his home in Scotland at the age of 75

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Special Articles

INSTITUTIONAL CARE OF THE MENTALLY ILL

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THERE is good reason to believe that as a result of advances in treatment and improved domiciliary and outpatient care, the size and character of the population of mental hospitals will gradually change Yet the institutional care of the mentally ill remains, and is likely to remain for some time, one of the most intractable problems of the medical service Not only are the existing buildings and staff inadequate, but it is by no means obvious in what way we should seek to improve them For although we are no longer content to regard the mental hospital as a general hospital grafted on to an asylum, there is still no satisfactory basis for decision about the optimum size, type, and location of mental hospitals, and their relationship to general hospitals

In the third report of the World Health Organisation's Expert Committee on Mental Health (1953), attention was drawn to the desirability of classifying patients in mental hospitals "into groups which are homogeneous from the point of view of the patients' therapeutic needs and their capacity for social adaptation ", and it was suggested that " the hospital should be composed of a group of small buildings, rather than a single block " In view of the immense diversity of needs of patients in mental hospitals, this seems to us much the most promising approach It was the approach proposed by the Webbs (in the Minority Report of the Poor Law Commission, 1909) when confronted with that other large population with diverse needs, the aged sick " It is a necessary preliminary of any effective reform to break up the present unscientific category of ' the aged and infirm ' and to deal separately with distinct classes according to the age and mental and physical characteristics of the individuals concerned " The present report summarises the results of an inquiry which attempts to apply this principle to the study of the institutional provision for the mentally ill

During 1957 the medical, nursing, and social needs of each of the 3555 Birmingham residents in mental hospitals were assessed by the psychiatrists responsible for their care The methods have been described fully elsewhere (Garratt, Lowe, and McKeown 1957, 1958) Here we use the data in an attempt to answer three questions

1 What facilities should be grouped together?
2 What type of accommodation should be provided?
3 Which patients need to be supervised?

The first question is concerned with identification of the major units needed, and the second with the arrangement of accommodation within each unit The third question is perhaps less obviously related to hospital design, but we shall suggest that the amount of supervision which patients need because of their mental state should have a considerable bearing on their grouping

Hospital Facilities

Experience of an earlier investigation of the chronic sick (Lowe and McKeown 1949) suggested that after assessment of their needs patients in mental hospitals could be divided into three classes according to whether they required full, limited, or no hospital facilities

459 patients (13% of 3555) were held to need *full hospital facilities* because they required frequent medical attention, skilled nursing, or ready access to laboratories, X-ray departments, operating-theatres, &c Most patients in this class were, of course, under active investigation or treatment, and needed several of the services which we have listed as alternative qualifications for inclusion 380 (83%) were being treated for a mental illness almost all were continent and fully ambulant, but they all needed skilled nursing, and about 1 in 8 needed basic nursing (washing, dressing, feeding, lifting, attention to bladder and bowel, &c) as well The other 17% were being treated for a physical illness (pulmonary tuberculosis, cardiovascular disease, traumatic and orthopædic conditions, &c.) most of them were confined to bed and many were incontinent, they all required skilled nursing and almost all required basic nursing

2655 patients (75% of 3555) were held to need *limited hospital facilities* They did not require the services referred to above, but needed either supervision because of their mental state or the simple attentions referred to as basic nursing 87% had a mental illness without physical complications most of them were ambulant and needed supervision and occupational training but little nursing, and about a quarter were capable of productive work The other 13% were physically ill (more than half were elderly senile patients) most of them were bedfast and needed both basic nursing and supervision

441 patients (12% of 3555) were held to need *none of the traditional hospital services* They did not require investigation, specific medical treatment, or skilled nursing (services demanding full hospital facilities), and they had neither physical disability serious enough to require basic nursing, nor mental abnormality for which supervision was necessary (services demanding limited hospital facilities) Their circumstances were analogous to those of patients in hospitals for the chronic sick who do not need continuous medical or nursing care but remain in hospital chiefly for social reasons It should be made clear, however, that not all these patients were suitable for discharge, even if they had had a suitable home About half were thought to be unable to live wholly independent lives While they needed none of the traditional services which hospitals provide, some of them needed occasional psychiatric supervision and assistance with such matters as training and employment

For the purpose of hospital planning for the mentally ill the three classes identified above seem to us the most fundamental they distinguish patients who need the facilities of a modern hospital from those who need only simple personal attentions and from those who need neither It would probably be agreed that on grounds of efficiency and cost it would be desirable to provide separate accommodation for these classes We do not, of course, imply that they are homogeneous, and under " accommodation " and " supervision " we discuss the possibility of subgrouping which might be reflected in the design of the accommodation But in relation to the facilities of the unit in which they should be placed, patients in each of the classes have more in common with others in the same class than with any in a different class

Accommodation

The type of accommodation to be provided within each of the three main units should, we suggest, be determined primarily by whether patients are ambulant or bedfast. Present conceptions of hospital design are so dominated by the general hospital that people tend to think almost exclusively of traditional ward systems, varied chiefly in respect of the number of beds in each ward unit. But, although suitable for short-stay patients who are bedfast most of the time they are in hospital, this arrangement is wholly inappropriate to the needs of long-stay ambulant patients, who need accommodation with a much higher ratio of dayroom (and other amenities) to bed space. We shall refer to this as hostel type of accommodation.

Of the total mental-hospital population of 3555 patients which we surveyed 84% were fully ambulant. This proportion does not include ambulant patients who were recently bedfast and had therefore needed traditional ward accommodation at a recent stage of their illness. Nor does it include partly ambulant patients, such as the "aged and infirm", for some of whom the hostel type of accommodation would be preferable. In the three main classes of mental-hospital patients (those needing full, limited, and no hospital facilities), the proportions of fully ambulant patients were 78%, 82%, and 98% respectively. These are evidently minimal estimates of the scope for non-traditional accommodation in each type of unit.

Supervision

At the present time patients in mental hospitals are by no means always grouped according to the amount of supervision they need because of their mental state, and patients with considerable insight may share wards with others who are seriously disturbed. From the point of view of staffing this mixing of patients is not a serious disadvantage, because all nurses are recruited to mental hospitals for the care of the mentally ill. But the situation would be entirely different if, as will be suggested later (McKeown 1958), mental hospitals were placed in such a relationship to the general hospitals that much of their nursing was done by nurses trained or in training for the general register. It would probably not be considered desirable for general-trained nurses to deal with disturbed patients, but there could be no reasonable objection to their attending patients not needing supervision. An estimate of the proportion of patients in mental hospitals who do not need supervision is therefore in effect an estimate of the extent to which nurses with a general training could contribute to the institutional care of the mentally ill.

Of the whole mental-hospital population (3555 patients) 14% needed no supervision whatsoever, and a further 42% needed no supervision so long as they remained within the hospital grounds. Patients in both these groups would be suitable for care by nurses trained for the general register. The proportions of unsupervised patients identified within each of the three main units (full, limited, and no hospital facilities) were 57%, 49%, and 100% respectively.

Suggested Grouping of Patients

The table shows the grouping of patients obtained by applying the criteria described above to the total Birmingham mental-hospital population. To make the figures more generally applicable, the results, based on the Birmingham population of about 1,100,000, are given as rates per 100,000.

There are, of course, differences of opinion among psychiatrists about two of the criteria on which the estimates are based—namely (*a*) the possibility of treatment (which has some bearing on the classification according to facilities required), and (*b*) the amount of supervision needed. (The other feature—type of accommodation—being based on mobility, is objective.) Since a considerable number of psychiatrists took part in the investigation, the estimates are probably fairly representative of contemporary opinion. However the figures are less important than the general principles on which the classification is based. Moreover, it is only in respect of the amount of supervision needed that substantial differences of opinion are likely. These differences would not affect the two main considerations—the identification of the three major units, and the type of accommodation within each.

DISTRIBUTION OF PATIENTS IN BIRMINGHAM MENTAL HOSPITALS (PER 100,000 RELATED POPULATION) ACCORDING TO TYPE OF HOSPITAL FACILITIES, ACCOMMODATION, AND SUPERVISION NEEDED

Hospital facilities needed	Accommodation needed	Supervision		Total
		Needed	Not needed	
Full	Traditional ward Hostel-type	8 11	1 22	9 33
Limited	Traditional ward Hostel-type	27 97	5 112	32 209
None	Hostel		40	40

The main application of the results of an inquiry such as this is in the planning of future hospitals. If the principles of classification and the suggested groupings are accepted, separate units should be provided for the patients in each of the three main classes, and the design of accommodation within each unit should be varied in relation to patients' mobility and need for supervision. The siting of the separate units—whether on the same or on a different site—and their relationship to the general hospitals will be considered separately (McKeown 1958).

Since there is little prospect of much new hospital building in the immediate future, it may be asked whether our findings have any bearing on the arrangements for the present hospital population. They do not seem to us to suggest that the patients needing full hospital facilities should be removed to general hospitals, leaving the mental hospitals to cope with the long-stay patients. Such an arrangement would establish divisions between staff as well as between patients, one group of psychiatrists being concerned with short-term remediable illnesses, and another being left with the less rewarding, but socially no less important, task of caring for chronic psychotic and senile patients. A more attractive possibility is an improvement in the facilities for the care of patients in the third class, who do not require hospital accommodation. The existence of such patients is well recognised, and the report of the Royal Commission (1957) proposed that in future they should be placed under the care of local authorities. Our data give some idea of the extent of the provision which would have to be made if this proposal were accepted, and show the nature and variety of the needs of the patients who could conceivably be transferred.

Summary

After assessment of their medical and social needs, the 3555 Birmingham residents in mental hospitals were classified as follows

(*a*) Patients needing the full range of hospital facilities (13%)

(*b*) Patients needing only limited hospital services, consisting of supervision because of their mental state or basic nursing (75%)

(*c*) Patients needing *none* of the facilities traditionally associated with hospitals (12%)

It would be well to accommodate these classes in separate units, and the design of each unit should have regard to the high proportions of fully ambulant patients (78%, 82%, and 98% in the three classes respectively) who need a high ratio of dayroom and other facilities to bed space

In grouping patients within the units account might also be taken of the proportions of patients (57%, 49%, and 100% respectively) who need no personal supervision, and could be cared for by nurses without experience of mental illness

We are indebted to the medical superintendents (Dr J J O'Reilly, Dr I A Macdonald, Dr C E Roachsmith, and Dr C M Ross) and staffs of the four Birmingham mental hospitals for their full cooperation in assessing the needs of their patients, and to the Birmingham Regional Hospital Board for a contribution towards the expenses of this inquiry *We are also grateful to Dr F C Edwards and Dr R H Cawley for helping to complete the record cards*

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Public Health

TOXIN FOOD-POISONING CAUSED BY FRIED POTATOES

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CITY AND PORT OF LIVERPOOL

The interest of most outbreaks of food-poisoning lies in the circumstances which result in infection Many accounts emphasise the importance of foodstuffs of a particular kind, mainly those derived from milk or from meat There is, however, a special interest when an extremely common foodstuff is shown to be the vehicle of infection Potatoes have very rarely been considered seriously as a possible cause This may be because there may have been doubts about whether potatoes are likely to act as a satisfactory bacterial medium

In 1955 we reported an outbreak of staphylococcal toxin food-poisoning caused by new potatoes infected after cooking and stored for two days before reheating and consumption (Davies and Parry 1955) We have recently traced a further smaller outbreak of staphylococcal toxin food-poisoning which, in this instance, was caused by contaminated chipped potatoes This outbreak and subsequent experiments are reported to emphasise that such common foodstuffs may be responsible for food-poisoning, especially if, after cooking or partly cooking, the potatoes are stored under unsatisfactory conditions

History of Outbreak

8 persons developed acute diarrhœa and abdominal pains, with vomiting in 2 of them, after a meal at a restaurant in Liverpool on the afternoon of Sept 21, 1957 The first 4 cases were reported from York and occurred among persons who had taken a meal in the restaurant while travelling to York 4 further cases were traced among Liverpool residents 2 of the persons were ill enough to be admitted to hospital, and the 6 others were acutely ill for at least some hours

In the 2 cases in which bacteriological examination of stools and vomit was undertaken promptly, *Staphylococcus aureus* was found (the stools showing a heavy growth) This finding, coupled with an incubation period of $^1/_2$–$4^1/_2$ hours provided the evidence on which staphylococcal toxin food-poisoning was diagnosed

In all 8 cases the meal had consisted of fried chipped potatoes and peas with either fish, lamb, or pork, followed by ice-cream in 7 cases, tea, or coffee The only foods common to all the victims had been chipped potatoes and peas Specimens of partly cooked chipped potatoes and cold lamb were found to be infected by *Staph aureus* Two tins of peas from the same batch were examined chemically and bacteriologically with negative results Thirteen swabs from kitchen utensils were also examined, with negative findings

Throat, nose, and hand swabs and fæcal specimens from the fifteen members of the restaurant staff were examined bacteriologically Eleven were carrying staphylococci

2 persons with positive hand swabs alone
1 „ „ „ throat swabs alone
3 „ „ „ nasal swabs alone
2 „ „ „ hand and nasal swabs alone
2 „ „ „ throat and nasal swabs alone
1 „ „ „ hand swab and fæcal specimen

The person who cooked the meal had, on hand and chin, septic spots from which staphylococci were isolated *3 other* members of the staff had septic cuts on hands and face In none of these instances were waterproof dressings used, as instructed by the Food Hygiene Regulations, *1955*

Epidemiological Investigation

The investigations suggested that the chipped potatoes might have been responsible for the outbreak, and careful inquiry at the restaurant showed that it was the daily practice to prepare chipped potatoes by hand This was done by the cook mentioned above, from whom large numbers of *Staph aureus* were grown from an uncovered cut on his left thumb and from his fæces

Having chipped the potatoes he partly cooked them for 1–3 minutes in ground-nut oil at a temperature of about 350°F The chips were then taken out of the oil and left exposed on a wooden tray in the kitchen The final cooking (lasting 5–8 minutes) did not take place until they were required for a customer's meal, usually later the same day, but it was not denied by the restaurant staff that chips had, at times, been left for more than twenty-four hours, having been partly cooked, until finally used The restaurant staff were vague about what had happened during the time immediately before the infected meal, but agreed that the partly cooked chipped potatoes may have been stored in the kitchen for 24 hours or longer

It is interesting to consider how the chips may have become infected Such a high proportion of the kitchen staff infected as carriers suggests that ample opportunity must have existed for contamination

If, however, the cook who prepared the chips initially had infected them, then it would seem reasonable to expect that the initial cooking for 1–3 minutes at 350 F would kill any staphylococci on the chips On the other hand, if the chips had been infected, after having been partly cooked, by handling or by aerial contamination from a nasal carrier, would the staphylococci be likely to multiply on the greasy surface of a partly cooked chipped potato?

In an attempt to find an answer to these important questions, experiments were designed in which chipped potatoes were artificially infected

Experiments

The following tests were devised to examine the degree of staphylococcal survival on cooked chips under café conditions

Test I—Eighteen chipped potatoes, each weighing 5 g and all being of equal size, were each inoculated with 0 1 ml of a suspension of *Staph aureus* The inoculum was allowed to soak into the chips for ten minutes They were then partially cooked in ground-nut oil for two minutes at 320°F They were then examined bacteriologically and found to contain no viable staphylococci

Test II—Fifteen similar chips were inoculated and partly cooked as in test I They were then divided into five equal portions, each of three chips These were all reinoculated with 0 1 ml of the same staphylococcal suspension and examined bacteriologically after 1, 5, 12, 18, and 24 hours The accompanying table shows that all were contaminated with large numbers of *Staph aureus*

Test III—A further fifteen chips, similarly divided, were inoculated, partly cooked, reinoculated, and left for 1, 5, 12, 18, and 24 hours as in test II At the end of each period the chips were boiled in ground-nut oil for three minutes at 320°F On bacteriological examination all were found to be sterile except portions 1 and 3 (examined after one and twelve hours respectively), in which sporing organisms were discovered

These three tests showed that cooking the chips for 2 or 3 minutes at 320°F killed all staphylococcal organisms, but in test II subsequent reinfection of partly cooked chips led to the recovery of staphylococci up to 24 hours later

BACTERIOLOGY OF CHIPPED POTATOES ARTIFICIALLY INFECTED WITH *Staph aureus*

Test no	Description	Time		Bacteriologial results
		Hours	Mins	
I	18 chips divided into 6 portions, each of 3 chips, inoculated with *Staph aureus*, boiled in ground-nut oil at 320°F for two minutes	—	1	Negative
		—	2	"
		—	3	"
		—	4	"
		—	5	"
		—	6	"
II	15 chips divided into 5 portions, each of 3 chips, inoculated with *Staph aureus*, boiled in ground-nut oil at 320 F for two minutes, then reinoculated	1	—	*Staph aureus* ++++
		5	—	" " ++++
		12	—	" " +
		18	—	" " ++++
		24	—	" " +++
III	15 chips divided into 5 portions, each of 3 chips, inoculated with *Staph aureus*, boiled in ground nut oil at 320 F for two minutes, reinoculated left for varying periods, and finally fried at 320 F for three minutes	1	—	Sporing organisms +++
		5	—	Negative
		12	—	Sporing organisms +
		18	—	Negative
		24	—	Negative

++++ very large numbers of organisms
+++ large numbers of organisms
++ moderate numbers of organisms
+ small numbers of organisms

To determine how fast staphylococci would multiply within 24 hours of reinfecting partly cooked chipped potatoes, test IV was made

Test IV—A quantitative analysis was made as follows

(1) Four chipped potatoes, all equal in size and each weighing 5 g, were inoculated with 0 1 ml. of the same suspension of *Staph aureus* They were left for ten minutes and then minced, weighed, and quantitatively examined The result, expressed as an average of 20 grammes, was 118,000 staphylococci per g

(2) A similar weighed quantity of chipped potatoes was inoculated with 0 1 ml of the same suspension of *Staph. aureus* as in previous tests After ten minutes the chips were partly cooked in ground-nut oil for two minutes at 320°F They were then reinoculated with a similar amount of *Staph. aureus* and left for 24 hours on a wooden tray The room temperature during the 24 hours averaged 73°F (conditions comparable with those found in many café kitchens). At the end of this 24-hour period the four chips were minced, weighed, and quantitatively examined The result, expressed as an average of 20 grammes, was 178,000,000 staphylococci per gr This is an approximate thousand-fold increase per organism per 24 hours

Discussion

The tests described above showed that initial cooking of chips destroyed any contaminating staphylococci Final cooking also destroyed any staphylococci which had been introduced after the initial cooking. The tests further showed that not only was it possible, successfully and easily, to reinfect partly cooked chips but also the rate of multiplication of the infecting organism, when these infected partly cooked chips were left at room temperature, was considerable

These tests show that the partly cooked chipped potato is a perfectly suitable medium for the growth of staphylococcus

Likely Cause of Outbreak

What probably had happened was that the chips were infected after being partly cooked. They were then left for long enough time to enable rapid multiplication of the staphylococci with simultaneous production of enterotoxin The final cooking would almost certainly kill all staphylococci remaining on the chips but would be unlikely to have much effect on the heat-stable enterotoxin which would be left in the chips and would cause the food-poisoning

Preventive Measures Possible

Every investigation of food-poisoning should suggest methods of prevention The faults which lead up to this small outbreak are well known

(1) Storage of partly cooked food when warm.

(2) Lack of realisation that subsequent heating sufficient to kill pathogenic organisms is insufficient to destroy the heat-stable enterotoxin of the staphylococcus,

(3) Faulty methods and hygiene in relation to infected sores, &c

Summary

An outbreak of staphylococcal toxin food-poisoning spread by chipped potatoes is described.

The dangers of partly cooking such potatoes and leaving them open to contamination are emphasized. Subsequent

cooking destroyed the staphylococci but not the enterotoxin which caused the outbreak

Experiments undertaken with artificially infected chipped potatoes are described They confirmed that a partly cooked chipped potato could act as a satisfactory medium for the growth of staphylococci Within 24 hours it was estimated quantitatively that the staphylococci had increased a thousand-fold

We wish to thank Prof Andrew B Semple, medical officer of health, City and Port of Liverpool, for his interest and permission to publish, and Prof D T Robinson, Dr E C Armstrong, and Mr D Peden, of the Public Health Laboratory Service, Liverpool, for the bacteriological testing and the quantitative analysis

REFERENCE

Davies, J B M, Parry, W H (1955) *Med Offr*, 94, 45

Deaths in Poliomyelitis-vaccine Laboratories

Two technicians in the Connaught Laboratories in Toronto, where poliomyelitis-vaccine experiments are carried out, have lately died after being bitten by monkeys It is not clear from the report [1] whether the monkeys were thought to be infected The first technician was bitten in October and died of suspected encephalitis four weeks ago The death is being investigated, the director of the laboratories has said that it is difficult to connect it with the bite The second technician was bitten "some weeks ago" but showed no sign of illness till March 16 He died, probably of encephalitis, four days later A necropsy and an inquest are being held

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[1] *Times*, March 22, 1958

Case of Smallpox in Liverpool

An Indian seaman on the liner *Circassia* was found to have confluent Asiatic smallpox when the ship anchored off Liverpool on March 19, he is now seriously ill in the smallpox hospital, Rock Ferry, Liverpool The sickbay attendant was admitted with him as a close contact, though he has shown no signs of the disease Nobody else on the ship has any signs of illness, all 400 have been vaccinated and given warning postcards, and warning letters have been sent to the medical officers of health in all areas in the British Isles where passengers or crew intend to go The patient speaks no English, and it is uncertain whether he was ever vaccinated He is thought to have been infected in Bombay

Tuberculosis in Refugees

According to a statement issued by the Joint Tuberculosis Council, about 7000 of the 15,500 Hungarian refugees remaining in this country have had chest radiographs, the prevalence of tuberculosis in them seems to be about 8 per 1000 This figure may include some observation cases, but the prevalence seems to be about two to three times that found in recent British surveys The Council estimates the number of active cases still undiagnosed at 50–100

The Council believes that much difficulty would have been avoided if the refugees had been radiographed on first reaching their transit camps, and suggests that in any future similar emergency mass-radiography units should be set up, with interpreters, at transit camps, it should be explained to the refugees that if tuberculosis is found they will not be sent home, and that treatment will be free and will probably render them fit within a few months If radiography were treated as a matter of established medical routine, says the Council, the question of compulsion need not arise

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Before Our Time

NIKOLAI ECK

THE interest in the treatment of portal hypertension by portacaval anastomosis in the last few years led to the publication of a translation of Eck's original paper [1] This paper, written in 1877, concluded with the sentence, "I had to postpone further experiments because I was called to join the active army" Of Eck's subsequent life little is known in the Western countries and reference books do not give the date of his death, which occurred just half a century ago, in 1908 Some further information about his life has now been supplied to Prof R Milnes Walker by Professor Kupriyanov of Leningrad, who has written the following notes

Nikolai V Eck was born in Petersburg in 1848 His father was a famous professor of medicine, Vladimir E Eck, a member of the Military Medical Academy He studied at the same Academy and in 1871 got his degree with honours, receiving "The prize of Prof Ivan F Bush" While an undergraduate he was awarded a gold medal for his paper on laryngeal polypi

On graduation he continued his studies at his father's Medical Clinic, at the same time qualifying as an extern in surgery and gynæcology In 1874 N Eck made a report and demonstrated a patient at a meeting of the Society of Russian Physicians in Petersburg The patient had had a myoma of the uterus, the tumour, weighing 4 5 kg, was surgically removed by the abdominal route It was the first surgical operation of that nature successfully performed in Russia In 1877 he published the description of a successful removal of interstitial uterine myoma, his publication being the first one in world literature

In 1877, while experimenting in the physiological laboratory of Prof I R Tarkhanov of the Military Medical Academy, Nikolai Eck suggested the technique and surgically achieved the portacaval anastomosis in a dog to abolish portal hypertension in hepatic cirrhosis According to his daughter, Miss Zinaida N Eck (now living in Leningrad), in 1889–90 N Eck made a portacaval anastomosis in a female patient suffering from some hepatic trouble The patient was said to recover, but there have been no publications concerning that case in medical literature

In 1882 Nikolai Eck successfully resected the pyloric end of the stomach in a case of cancer of the stomach, he demonstrated that female patient in the Society of Russian Physicians in May, 1882, and published a paper on it In the concluding part of the paper he stated

> "If there arises the necessity of resecting the stomach together with a part of the large intestines, a considerable portion of the stomach being involved, as well as in the case of cancer affecting a large portion of the stomach, other structures not being involved, one should not make a duodenal fistula after Wölfler's method Even if it were impossible to join the edges of the stomach and the intestine, one should securely close the duodenum with sutures, and connect the pars cardiaca of the stomach with the portion of the jejunum adjacent with the duodenum by placing it in front of the colon, or by making an orifice in the mesocolon transversum The latter method being the better in my opinion"

Thus Nikolai Eck gives a description of a surgical method which was three years later, in 1885, recommended by *Billroth*

After 1880 Nikolai Eck started investigating problems of sanitation and hygiene, which resulted in a paper entitled An Attempt at Analysing Death-rate Statistics in Russia, published in 1888, this was his last contribution to medical sciences Being a widely educated man, well read in different domains, N Eck was interested in various branches of knowledge, and in his later years published a number of papers on ethnography, geography, and geology

In 1884 there was a report on the results of a mission to Egypt during an epidemic of cholera, and in 1889 a paper on the possibilities of exploiting silver-lead and zinc deposits near the Kuban river His last contribution was in 1893, entitled On Roadways to Sukhum-Kale and on a Narrow-gauge Branch Railway to Karatchai for the Elbrus Company Mines

He died in 1908 and is buried in Leningrad

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[1] Child, C G *Surg Gynec Obstet* 1953, 98, 375

In England Now

A Running Commentary by Peripatetic Correspondents

As a mere doctor I accepted the invitation to a meeting of a purely scientific society with some diffidence, and inspection of the programme did little to lessen my misgivings. I need not have worried. It is true that to me many of the communications would have been equally intelligible in Chinese. But two papers paid for all. One concerned the effect of certain pharmacologically active agents on peristalsis in the mouse. This was measured by counting the droppings and noting their consistency. After 5-hydroxytryptophane, I learnt, there was an increased yield which could be related to the logarithm of the dose and a change of consistency rather like that produced by senna-pod tea. An impressive colour photograph left no doubt that the technique combined simplicity with elegance, and anyway it has been well said that to the impure all things are scientific.

But it was an earlier paper that really gripped the audience, partly because it was given by an engineer and so was presented with a clarity which eludes most medical graduates. He wanted to find out if men could fly, he said, and the first question to settle was how many horse-power the human engine could generate. A simple enough question in all conscience but could his listeners tell him the answer? No, they couldn't, so he had to tackle the job himself by suspending bicycles plus riders in wind tunnels. It seems that most of the work done by a cyclist is spent in overcoming wind-resistance and that he would get along much faster in the horizontal position especially, the engineer ended thoughtfully, if he could work a second pair of pedals with his hands. In the ensuing discussion it seemed to me that the audience was fighting shy of putting the obvious question to a layman who had already floored his scientific colleagues. One member thought that the pioneer work of Da Vinci might have been mentioned, another felt that Leonardo in turn owed much to the more experimental, if ill-starred, approach of Icarus, and for myself I noted with regret that the contributions of the late W. Heath Robinson seemed to have been forgotten.

Finally someone screwed up enough courage to ask the engineer if he thought that man would ever be able to fly. "Well," he replied cautiously, "it all depends on how long he wants to stay in the air." At this point the society adjourned for lunch, and we are still wondering whether a practical solution to the traffic problem is at last in sight or whether it is still all in the mind.

* * *

Yesterday, as I cycled to the hospital I passed a cycle-pedal lying in the middle of the road. It appeared intact and in good order, there were no signs of the rest of the cycle, or any other related bits and pieces lying around. I spent the rest of my ride wondering how it had got there.

It could not, I thought, have just dropped off and not been noticed, and yet if it had been noticed surely the owner would have stopped and gone back for it. Perhaps he had stopped and gone back, tried to replace it, failed, and just chucked it down again—in the middle of the road? It did not seem likely. Otherwise if he had stopped at all, he must have carried it off—in his hand—in his pocket—wherever a loose cycle-pedal most conveniently went. Yet a loose cycle-pedal was not a very convenient thing to carry round, perhaps after all he had just chucked it down. If he was the sort of chap, though, to throw cycle-pedals wildly round the roads, wouldn't he almost certainly have despaired completely and left the rest of the cycle there too?

My ward-sister thought that he must have noticed it come off, but she seemed unsympathetic about the whole affair. "How on earth," she asked, "could anyone in their right senses continue cycling using one pedal and their other foot left thrashing the air? He probably tried to retrieve it, but the traffic was too heavy, so that he was forced to leave it there." But I don't agree. I really think he just did not notice and went cycling on (perhaps it was downhill), arrived at work, put the machine away, and started work before suddenly a vague disquiet about his transport assailed him, rapidly followed by more precise feelings of loss. In fact I know he did. I had to have a new pedal put on my cycle that very day.

* * *

There was some difference of opinion in the firm about polio immunisation. The enthusiasts were in favour of immunising our own patients, whilst the lethargic felt disposed to leave it to our public-health colleagues on the grounds that it saved us trouble and that a bit of clinical work was no bad thing for the M.O.H. anyway.

Inevitably lethargy gave way to enthusiasm, and at first, as the Ministry disgorged minimum quantities of vaccine slowly and sporadically, it seemed that no great strain threatened disruption of the practice organisation. Then without warning the health area office announced that our next quota was 400 doses and would we please collect as soon as possible. The lethargics' satisfaction in being able to say "I told you so" was offset by contemplation of the awful alternatives: 400 mothers and offspring going through the surgery premises in one day like a swarm of locusts, or even worse weeks of disruption as wailing children and fainting mothers cluttered up every surgery hour. It was the leading lethargic who thought of the answer—hire the community centre, borrow a health visitor and a district nurse, and knock off the 400 in a day without disorganising a single surgery. So 400 letters went out inviting batches of 50 every half hour from 9 A.M. to 12.30 P.M. on the appointed day.

When the day came, two receptionists did the clerking in the assembly hall and provided each victim with an immunisation record card. The health visitor shepherded 2 victims at a time into an adjacent room where 2 of us immunised for two hours until relieved by the remaining 2 partners. Nurse kept us supplied with sterile needles and syringes from a fish-kettle boiling on a gas-ring, and distracted the attention of the more nervous victims by brandishing a kidney dish of gaily coloured sweeties as an impending reward. It didn't stop all of them from giving tongue, and one angry young man both howled and helped himself to a handful. But to our surprise we finished well ahead of schedule and could easily have coped with another 100 before lunch.

On the other hand the operation cost us 1 lb. of liquorice-allsorts, 2 large tins of 'Smarties', 1 box of 'Maltesers', and 2 lb. of jelly babies.

* * *

I have always held that the Romans got the genders of light and sound wrong. They made *lux* feminine, whereas its positive, direct, and calculable nature clearly deserved the masculine gender. *Sonor* should have been feminine, not masculine, because of the astonishing and unpredictable variations in its behaviour. Let me illustrate the point. My consulting-room is on the ground floor of my home and has a well-made door which has hitherto given satisfaction in sound exclusion. But the other day, when I was in the middle of a sigmoidoscopy on a lady patient, the voice of our daily help (who was cleaning the hall) was suddenly heard with dreadful clarity—as though she was in the room. Her words, addressed to my wife on the first-floor landing, added to my distress: she said "I can't find the long-handled brush, Ma'am."

* * *

News from School.—Last night we had a string orchestra who ended their somewhat patchy concert by playing *eine kleine Nachtmusik* at volumes ranging between *ffff* and *ffff*. This did not add to the faery effect. They seemed to enjoy it, and the school, in a somewhat cynical mood, gave them about five minutes of applause interspersed with such exclamations as 'Oley!' or "Viva!" They suspected nothing and went out waving.

I spent some of yesterday afternoon on an incredibly boring committee meeting and the rest wandering round the market and Woolworths. I was looking for a plant. When my old one died I thought I would never have another, but, after all, a plant is a plant. However, I failed to find one that approached my tulip in interest or beauty. Most of those I saw were in bud, and just waiting to burst into minute and sickly flowers. 2*s.* 6*d.* without pot.

Letters to the Editor

ESTIMATING FŒTAL MATURITY

SIR,—Your leading article of Feb. 1 on the radiological estimation of fœtal maturity made heartening reading to any radiologist who has shown especial interest in obstetric radiology. I should like to share in your appreciation of Dr Blair Hartley's work,[1] and I am most interested to learn that the times of appearance of certain epiphyses do not vary as widely as formerly believed.

From the inception of the full radiological service at Queen Charlotte's Hospital in 1941, it has been my custom to estimate the fœtal maturity routinely (when this was feasible without the necessity of taking additional radiographs) in making reports on pelvimetric examinations. That these estimates were of genuine value to my obstetric colleagues was shown by the increasing number of requests received specifically for the estimation of fœtal maturity. I relied mainly (though not entirely) on cephalometric data drawn up by Hodges.[2] In your leading article, Hodges' work is rather belittled, mainly because "there are large biological variations in the dimensions of the fœtus in the second half of gestation." I can hardly refrain from pointing out that, in medicine, we do not discard the evidence afforded by the pulse-rate, though this is indeed subject to wide biological variations.

Your article has prompted me again to inquire into the reliability of estimates of maturity based on cephalometric study using Hodges' data (with minor modifications which I have introduced over the past twenty years). A survey of 200 cases has been made, taken in strict alphabetical order from our record files of pelvimetric reports made between 1952 and 1956. In this series, the examinations had been made between the 31st and 40th weeks of pregnancy, the majority being at the 35th week.

The results are shown in the table: from cephalometry alone, the radiological estimated date of delivery (R.E.D.D.) was within a week of the actual date in 42% of the 200 cases, within two weeks in 72.5%, and within three in 86%. I suggest that these figures indicate that the estimation of maturity from cephalometry alone is a procedure of value.

RADIOLOGICAL ESTIMATE OF MATURITY BY CEPHALOMETRY ALONE: FINDINGS IN 200 CASES

Actual delivery related to R.E.D.D.	Delivery later than R.E.D.D.	Delivery earlier than R.E.D.D.	Total		
Within 1–7 days	45	39	84 (42%)	72.5%	86%
8–14 „	30	31	61 (30.5%)		
15–21 „	22	5	27 (13.5%)		
21–28 „	17	2	19 (9.5%)		
29–35 „	3	0	3	(4.5%)	
36–42 „	3	3	6		
	120	80	200		

It is of interest to note that the average infant birthweight in the 45 cases delivered more than fourteen days after the R.E.D.D. was 8 lb. 3 oz., and in the 10 cases delivered more than fourteen days before the R.E.D.D. it was 6 lb. 1 oz. In the former group, many infants were regarded as frankly postmature, and in the latter group 6 were regarded as premature. In estimating the maturity by the method I have used, a radiologist should indicate that the skull size is "*average* for a maturity of *x* weeks" or that "the maturity is *x* ±2 weeks."

Cephalometry certainly has its place in estimating maturity and, after Blair Hartley's work, I have a renewed interest in the epiphyseal ossific centres. A combination of both methods of approach could well lead to even greater accuracy in the estimation of fœtal maturity, provided that we remember that all human growth, both in dimension and maturation, is subject to considerable biological variation.

Queen Charlotte's Maternity Hospital,
London, W.6. E. ROHAN WILLIAMS.

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[1] Hartley, J. B. *Brit. J. Radiol.* 1957, 30, 561.
[2] Hodges, P. C. *Amer. J. Roentgenol.* 1937, 37, 644.

SEPTICÆMIA IN MODERN THERAPY

SIR,—Mr Slaney and Mr Brooke (March 8) report eight cases of septicæmia following surgery, in six of which cortisone was given. We have recently had two similar cases. One we are still grappling with, but I should like to record the details of the woman who unfortunately died.

A married woman, aged 38, had had moderately active ulcerative colitis for 6 years. While in the medical wards in 1952 she had a short course of corticotrophin, with temporary improvement. No further steroid was administered during the next 6 years.

In February this year it was deliberately decided, after consultation, that surgical treatment should be adopted. I must emphasise that the decision was not forced upon us because of any deterioration in the patient's condition.

She was thin but not emaciated. Hæmoglobin 86% (*Sahli*), serum-electrolytes normal. Albuminuria was found and she had an ano-vaginal fistula. Her bowels moved about 5 times during the daytime.

On Feb. 11 a proctocolectomy was performed, after the usual preliminary bowel sterilisation using phthalylsulphathiazole and streptomycin. To the naked eye the serosal injection appeared to terminate abruptly in the mid transverse colon, but later examination showed that the disease extended to the hepatic flexure. An ileostomy was established in the right iliac fossa, using perfectly healthy ileum, and the whole operation was conducted without complication. The bowel was not friable and did not tear at any time. Total blood-loss was less than one pint.

For the first 2 days after operation all was well. On the 3rd day her ileostomy acted, but only very slightly, and the discharge consisted of melæna. Her blood-pressure then fell (60/40 mm. Hg), she developed glycosuria and became jaundiced. Blood-culture on the 9th postoperative day yielded a heavy growth of *Escherichia coli*, sensitive to oxytetracycline, aureomycin (chlortetracycline), chloramphenicol, and sulphonamide, but resistant to streptomycin. She was given successively streptomycin and penicillin, tetracycline, and lastly erythromycin, but continued to have rigors, and died on the 15th postoperative day. Necropsy confirmed that she had had septicæmia, and bacterial endocarditis affecting hitherto undamaged mitral valve cusps.

In contrast to the accounts given by Mr Slaney and Mr Brooke, this woman, who in the first instance was by no means gravely ill, developed a septicæmia after a very straightforward operation: she had had no steroid therapy, and she succumbed despite treatment to an organism which was sensitive to several agents. It may be that our doses were not high enough; I note with interest the truly massive doses of penicillin used in Slaney and Brooke's case 1.

As this is our 2nd case of septicæmia within a month, it will be well for surgeons not only to heed the warning put so ably by our colleagues in Birmingham but also to ensure that treatment is at least adequate once this formidable complication has arisen.

I do not wish to take up the wider issue of why this complication appears to be commoner nowadays, but it does occur to me that the greater use of venepuncture, both in anæsthesia and in postoperative infusions, may be a hitherto unsuspected route of infection

Stobhill General Hospital,
Glasgow
F T CROSSLING

SIR,—I was particularly interested in the emphasis laid by Mr Slaney and Mr Brooke on steroids as an important factor in the development of septicæmia

In many skin departments steroids are widely used. On the whole we ourselves have seen few serious complications There has been, however, one case of septicæmia, in a man of 26 who had psoriatic arthritis and erythrodermia due to generalised psoriasis He had had steroids intermittently for months

He was admitted to hospital while taking prednisone, 15 mg t d s Shortly afterwards he became febrile and a blood-culture revealed *Staphylococcus pyogenes*, insensitive to penicillin, aureomycin, tetracycline, and streptomycin, sensitive to chloramphenicol and erythromycin Before the result was known he developed pain suggestive of a perforated peptic ulcer and had a laparotomy, at which nothing abnormal was found He responded well to erythromycin, 2 g a day, and chloramphenicol, 2 g a day, given for six days A few days later the temperature again rose, and blood-culture grew *Staph pyogenes*, insensitive to penicillin and aureomycin, sensitive to streptomycin, chloramphenicol, and erythromycin No antibiotics were given, and the temperature gradually fell to normal During this period the laparotomy wound became infected, a swab showed *Staph pyogenes*, insensitive to penicillin, aureomycin, and chloramphenicol, sensitive to erythromycin, and *Staph pyogenes*, insensitive to penicillin and aureomycin, sensitive to chloramphenicol and erythromycin

While he was very ill his skin improved, and it continued to do so afterwards, even when steroids had been withdrawn, in this case indeed the septicæmia ultimately did more good than harm During the episode his general condition was surprisingly good but he was mentally disoriented

In view of the universally moist and inflamed skin of patients with erythrodermia it is perhaps surprising that the complication appears to be rare This is fortunate, for it is in just such cases that steroids may be of great value, and admission to hospital difficult to avoid

The London Hospital E 1
C M RIDLEY

SINGLE DAILY DOSE OF CHLORPROMAZINE

SIR,—All Saints Hospital has for some years used the established tranquillisers as a long-term treatment of many of its psychotic patients, chlorpromazine being the most widely used It had been our custom to give this drug in divided doses two or three times a day, the commonest scales were 25 mg t d s and 50 mg t d s The nursing time involved in giving tablets on such a scale and more or less permanently was considerable With the kind support of the physician-superintendent, it was decided to try giving a group of patients their total daily requirements of chlorpromazine as a single morning dose

A small open ward, averaging 35 long-stay male patients, was chosen, under senior nurses who had known the semi-static population for a long time, both before and during their chlorpromazine treatment, and who were skilled in accurate observation from previous experience of research Most of these patients had been refractory for a long time before they improved on chlorpromazine, and all had had this treatment for many months One or two patients who were known to be sensitive to the drug were not at first included The corresponding female ward also cooperated but here the patient and staff population were more variable

For four months the nurses, ancillary staff and I watched the individual and social progress of the ward carefully, and had information from the various hospital departments in which patients worked and played and from their families No adverse effects of the change had been noticed at the end of this time, apart, possibly, from some slightly increased lethargy about an hour after administration of the tablets in one or two patients A number of other wards have now followed this policy with success

It does seem that where a patient's response to the divided daily dose of chlorpromazine has been established over a reasonable period it is safe and advantageous to give this as a single daily dose, at any rate where the total amount does not exceed 150-200 mg daily

All Saints Hospital
Birmingham 18
J C N TIBBITS

BUDGERIGARS AND POLIOMYELITIS

SIR,—Several mammalian encephalomyelitis viruses have been recovered from birds or infection by them deduced from the serological demonstration of specific antibodies—St Louis,[1] Japanese B,[2] Aujeszky's disease,[3] and both Eastern and Western types of equine encephalomyelitis (numerous references), but only the equine and Aujeszky viruses were recorded as having caused frank disease with histologically demonstrable lesions in the avian hosts, and the disease caused by the last of these viruses was entirely an experimental product

Veterinary neuropathologists will therefore be most interested in the preliminary communication from Dr Sommerville and his colleagues (March 8) It is a great pity the nervous system of the second budgerigar was not submitted to a detailed histological examination More than twenty diseases are known to afflict the nervous system of various avian species (human poliomyelitis is not yet one of them), and although several of these can be reasonably dismissed in this case, there still remains the possibility of neural lymphomatosis (to mention only one) having caused the paralytic symptoms in the budgerigars That the second budgerigar was no more than a subclinically affected host to the poliomyelitis virus, that the bird was infected by biting the boy, or that boy and bird were both infected from a common source, were not disproved, nor was any relationship between the poliomyelitis virus and the paralytic symptoms established

Ministry of Agriculture, Fisheries and Food,
Central Veterinary Laboratory,
Weybridge, Surrey
L M MARKSON

SIR,—In your issue of March 8 Dr Sommerville and his colleagues describe a boy who contracted fatal bulbar poliomyelitis thirteen days after being pecked by a budgerigar Poliovirus type 1 was found in fæces from the boy and budgerigar

We are very interested in their experience because in July, 1956, we came across a household in which a child developed paralytic poliomyelitis (poliovirus type 1 found in fæces), and in which several canaries had died about the same time

The child sickened on July 10, 1956, and was admitted to hospital three days later There was no definite history of being pecked by a bird, but she did play in the room in which they were caged

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1 Chamberlain R W, Kissling R E Stamm, D D, Sudia W D *Amer J Hyg* 1957, 65, 110

2 Hammon, W McD, Reeves W C, Sather G E *ibid* 1951 53, 249

3 Shahan M S, Knudson, R L, Seibold H R Dale C N *N Amer Vet* 1947 28, 440 511

The child's father kept canaries as pets and he had not, heretofore, been troubled by ill health among them The first canary died on July 12 after, he thought, two days' illness Within two weeks the remainder (22 in all) had expired He did not notice that before death any bird suffered paralysis of legs

No new birds had been brought into the house during the preceding three months so that the likelihood of infection being introduced from outside by an ailing bird can be discounted

Since the child's illness and that of the canaries appeared about the same time the possibility of a connection between them suggested itself

In the hope, therefore, that the cause of the deaths would be determined, a carcass plus excreta from the cages were transmitted to a laboratory outside this country We were disappointed when subsequently informed that because of pressure of work the specimens could not be examined

Though we cannot say the actual cause of the canaries' death, the circumstantial evidence at least suggests the possibility of poliomyelitis, and in view of the findings of Dr Somnerville and his colleagues the occurrence is considered of sufficient interest to record

Dublin City Health Department J B O'Regan
M Crowe

SYLLABUS FOR EXAMINATIONS IN PSYCHOLOGY

Sir,—I have read Miss Silver's letter (March 15) with considerable interest, and I entirely agree with her It would be only fair to Conjoint D P M candidates to issue an explicit syllabus, stating the precise requirements Otherwise, they are working in the dark

It seems as if the policy in part I has undergone a radical change during the past few years The questions in the psychology paper are more vague and less "textbook" The anatomy and physiology paper is now in two sections and questions "above the line" seem to be pure neurology, which is scarcely just to candidates unless they can be regarded as topics in experimental neurophysiology One of the questions last year requested details of the lives of Sherrington, Hughlings Jackson, Cushing, and Charcot Surely candidates are not required to read biographies in addition to all their other reading ?

The Conjoint Board should issue exact requirements for this diploma

Student in Psychology

"KWASHIORKOR" IN AN ADULT

Sir,—I was very interested in the discoloration of the hair in the patient suffering from kwashiorkor described in your issue of March 8 by Dr Krikler and Dr Schrire Their patient suffered from deficient intestinal absorption due to a side-to-side anastomosis of the lower ileum "His hair turned red while the malabsorption was at its worst, and reverted to its normal brown colour once he was cured by restoration of intestinal continuity" Later the authors observe "we can find no reference to such hair changes in steatorrhœa" They quote one example of such changes occurring in ulcerative colitis

In February, 1955, I saw a patient, aged 56, complaining of incessant fatigue, amounting occasionally to exhaustion, present since 1949 She had suffered during the same period from diarrhœa and anæmia Malnutrition had been suspected, and treatment with vitamins had helped but not cured her

In her youth her hair had been wavy, light brown, and very long and thick At the age of 19 she had meningitis, and thereafter her hair rapidly became grey When she was in her early thirties she began to develop bright yellow locks The locks were not permanent One part of her scalp would begin to grow yellow and so remain for a variable period eventually the roots would become grey and the yellow lock would "grow out", another lock meanwhile becoming discoloured At the time of my examination her forelock looked as though it had been dyed a very ugly brassy yellow

Investigation showed that she was suffering from steatorrhœa and she was given a gluten-free diet Her health was completely restored The yellow locks gradually "grew out" and have not re-appeared

I am unable to offer any explanation of this curious symptom, but presume it to have had the same origin as the red hair of the case described by Dr Krikler and Dr Schrire, modified by the fact that my patient originally had grey hair and theirs brown

London, W 1 Raymond Greene

PSYCHOSIS AND TREMOR DUE TO MECAMYLAMINE

Sir,—I wish to report briefly a case in which psychosis, tremor, and hyper-reflexia were similar to the findings of *Dr Harington and Dr Kincaid-Smith (March 8)*

A man of 50 was admitted on Dec 10, 1956, after a su arachnoid hæmorrhage He was confused and disorien but there were no localising signs in the central nerv system His blood-pressure was 240/140 mm Hg an blood-urea 126 mg per 100 ml

On Dec 27 he was rational and his blood-pressure ha settled to 170/90 It rose to 200/130, and reserpine 0 25 mg six-hourly was given from Jan 2 There was little effect an on Jan 9 the blood-pressure was still 210/130, mecamylamin 2 5 mg q d s was prescribed

By Feb 1 the blood-urea had fallen to 85 mg per 100 m and the blood-pressure to 150/90 Later the blood-urea ro to 130 mg per 100 ml , and because of its alleged action i increasing renal plasma flow hydrallazine 25 mg eight-hour was substituted for the mecamylamine on Feb 6

On the morning of Feb 11 the patient was found to b extremely confused, disoriented, and aggressive and thre his cup through a window On extension of the arms the was a typical "liver-flap" type of tremor, all tendon jer were very brisk, and there was bilateral patella and ankle clonu

The clinical picture was so classical that acute liver-failu was diagnosed and appropriate treatment started, but live function tests the following day were normal Blood-pressu remained at 140/80 but the blood-urea had risen to 302 m per 100 ml and the hydrallazine was stopped Without trea ment the blood-pressure rose to 200/110 but the blood-ur fell to 46 mg per 100 ml and the patient was rational aga by Feb 17

He was discharged on March 1 and when last seen on July he was *symptom-free* and the blood-pressure was 190/100

In this case, the tremor was striking enough to give ri to a confident but wrong diagnosis of liver-failure, wi the mental changes and increase in muscle tone, the syn drome was identical with that previously described on *in liver-failure*

These cases had in common a high blood-urea, hyper tensive disease, and administration of nitrogen-containin drugs, the syndrome has not been described in untreate hypertensive disease with raised blood-urea The fac that our patient recovered reflects the lesser severity o the hypertensive disease, which also accounted for th smaller doses of hypotensive drugs

It seems possible that in the presence of renal failure a sufficient *quantity of* these nitrogenous substance could accumulate and act in the same way as the nitro genous substances (? ammonia) responsible for th syndrome seen in liver-failure

I wish to thank Dr P Edward Dipple for permission to repor this case

The Royal Gwent Hospital,
Newport, Mon
Richard C R Connor

SEPARATION OF MOTHER AND CHILD

SIR,—Dr Bowlby performs a great and continuing service to child psychiatry by focusing attention on the emotional life of the young child His views on separation (March 1), however, may need re-evaluation He regards "separation of young children from their mother-figures as a serious mental-health hazard" In his studies on separation [1] [2] he does not differentiate privation from separation, and this seems to invalidate his findings Privation can and does commonly arise even though the mother is present Privation need not arise without the mother Separation and privation are not synonymous terms

In 1944, in a study on the causes of delinquency,[1] he compared the histories of a group of "affectionless thieves" with a group of other delinquents Of the 14 "affectionless thieves", 12 had separation experiences of over six months Dr Bowlby concluded that a break in the continuity of the mother-child relationship had resulted in more or less permanent impairment of the ability to make relationships More striking, however, than the history of separation is the severe privation to which these children were subjected both before and after the separations The circumstances making for privation before separation can cause an emotional disturbance in the child and also lead to separation Where separation brought relief, the children did not present at Dr Bowlby's clinic Where separation brought privation this aggravated the emotional disturbance and brought the child to attention From the facts presented in this investigation it seems that privation and not separation was responsible for the state of the children

Dr Bowlby's second investigation [2] also appears to confuse separation with privation and so invalidate his findings The variable of privation in the sanatorium was not controlled and any differences between the separated sanatorium children and the control group can as readily be due to privation in the sanatorium as to separation from the mother Furthermore, the variables of the pre- and post-separation histories of the two groups compared are not controlled, and additional methodological difficulties make it unlikely that the investigation could validly show differences between the two groups Dr Bowlby feels that the principal value of this investigation has been "to display the great heterogeneity of personality organisation which is consistent with having undergone a prolonged separation experience starting before the fourth birthday" But no control group was used in investigating the personality organisation, and it is reasonable to suggest that "great heterogeneity of personality organisation" is to be found in any group of children, separated or otherwise

That separation experiences are uncommon in young children and are not themselves a cause of mental ill health in children is shown by an investigation [3] in which a group of emotionally disturbed children and a control group of healthy children were compared for their separation experiences before the age of 5 years The separation experiences of the two groups were very similar Long separations before 5 years were uncommon in either group, in both groups, two thirds of the children under 2 years had not experienced separation of more than two days from their mothers It is not separation per se which causes mental ill health in children but the privation arising from the separation or, more commonly, the privation suffered while still with the parents

Privation arising from separation is to be deplored but is not an inevitable consequence of it The same investigation [4] studied the care of the children when away from home during separations In 62 out of 92 occasions of separation, the parents made adequate provision with relatives or friends On 26 out of 92 occasions the child was cared for in hospital and the care was harmful on most occasions Dr Bowlby's admirable work has done much to focus attention on privation arising from hospital admission In preventing privation it would be particularly rewarding to study the children, a minority, who benefit from a hospital admission

99 5% of children live at home,[5] and privation here is equally to be deplored No-one would question the value of loving care from an affectionate mother, but "normal home life" can be far from normal Clinical work suggests that degrees of emotional disturbance in children arise from degrees of privation while with some parents This is the major cause of mental ill health in children Relief for the children can sometimes, after careful investigation, come only by separation, either permanently or in the form of day foster care

The exaggerated emphasis on separation as an evil in itself has led to disturbing tendencies in child care, there is reluctance, in some quarters, to rescue a child suffering privation in his own home, there is some loss of confidence in the day nursery, nursery school, and fostering Great opportunities for preventive psychiatry appear to lie in the antithesis of Dr Bowlby's thesis

Department of Child and Family Psychiatry,
Ipswich

J G HOWELLS

ANTIBIOTIC PROPHYLAXIS

SIR,—It seems that Dr Platt (March 1) may have misunderstood the question under discussion In my letter of Feb 1 I mentioned that "the question is not what one uses as a prophylactic agent but whether chemoprophylaxis or antibiotic prophylaxis is justified, beneficial, and safe " Dr Platt has been using sulphaethylthiadiazole ('Sethadil') as a prophylactic, but he did not say why he had used it This sulphonamide is at present said to be of very low toxicity, but time and experience alone will prove its true value Moreover, my question (are sulphonamides in effective dose not more toxic and hazardous than penicillin?) was based on Dr Warren Crowe's prescription of sulphathiazole 1 g 4-hourly I hope Dr Platt will agree that penicillin in therapeutic doses is less toxic than sulphathiazole in these doses

Victoria Hospital,
Accrington

S S JHAVERI

LEUCOCYTE AGGLUTININS AND BLOOD-TRANSFUSIONS

SIR,—In your leading article of Feb 15 you say that the leucocyte agglutinins so far found are all iso-agglutinins, and that autoleucoagglutinins have not been convincingly demonstrated

Of course, the criteria for autoactivity of leucocyte agglutinins are subject to discussion Personally, I should be satisfied with the demonstration of

(1) Agglutination of the patient's own leucocytes (with proper controls provided), and

(2) Absorption of the leucoagglutinin with the patient's own leucocytes, followed by elution from the absorbing cells

These criteria were fulfilled in a study [6] of a case of monocytic leukæmia where an autoleucoagglutinin was present in the aleukæmic phase of the disease It is not claimed that this explains the mechanism of aleukæmic leukæmia, but in some cases it might be an important factor

Moreover, the very common occurrence of leucocyte agglutinins in patients with collagen diseases [7] is of much

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Bowlby J Int J Psycho-anal 1944, 25, 19
Bowlby, J, Ainsworth, M, Boston, M, Rosenbluth, D Brit J med Psychol 1956 29, 211
Howells J G, Layng, J Lancet, 1955, ii, 285
Howells, J G, Layng, J Med Offr 1956, 95, 26, 345

5 7th Report of the Children's Department Cmd 9881 H.M. Stationery Office 1956
6 Killmann S-A Acta haemat Basel 1957, 17, 360
7 Killmann, S-A Acta rheumat scand 1957, 3, 209

interest Some of these leucoagglutinins have been found in patients who have not been subjected to iso-immunisation with foreign leucocytes by transfusion or fœtal stimulation

It therefore seems that there is a case for the existence of autoleucoagglutinins

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SVEN-ÅGE KILLMANN

THE TWICE-BORN

SIR,—I found your criticism (Feb 22) of Dr Carstairs' book on a study of a community of high-class Hindus uninformative and disappointing Although critical, you do not tell us what the object of the study was nor anything about the results obtained It seems to me that these are, perhaps, the most important aspects that a review of a scientific study should mention and that to criticise a book without informing the reader about these is unfair to the author

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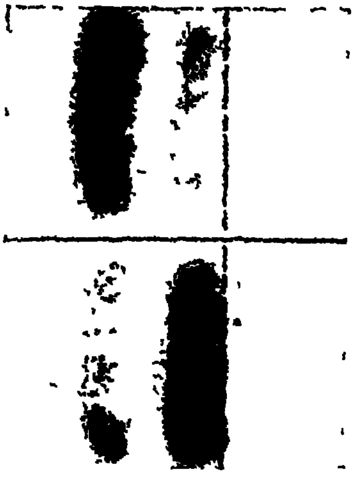
and Industrial Medicine,
University of Sheffield
JOHN PEMBERTON

LIPOPROTEIN PATTERNS IN MYOCARDIAL INFARCTION

SIR,—With great interest I read the comments by Dr Dagnall[1] and Mr Franglen[2] on the valuable paper by Dr Smith[3]

Dr Dagnall says that the β-lipoprotein level in the serum may be reduced in some pathological conditions Using paper electrophoresis we investigated the serum-lipoproteins in 81 blood-donors—i e, clinically healthy people We found an atypical lipoprotein pattern in 3 of them, where the α-lipoprotein accounted for more than 50% of all lipoproteins stainable with Sudan black (see fig) An inverse ratio of α- and β-lipoprotein may be seen, therefore, in some clinically healthy people



Serum-lipoprotein patterns (a) the lipoprotein pattern of human serum with the inverse relation of α- and β-lipids, (b) the typical pattern of lipoproteins

In previous investigations, during electrophoresis of lipids under the same conditions as for fractionation of serum-proteins, much of the β-lipoprotein was often absorbed in the paper during migration For this reason we modified the experiment and transferred the starting-point to the centre of a Whatman 3 mm paper strip, reduced the voltage, increased the ion concentration of the buffer (e g, by adding saline solution), and cut down the duration of electrophoresis Lipoproteins are separated far more quickly than the protein fractions By this procedure we succeeded in clearly separating both main lipoprotein fractions in the least possible space We abandoned the independent evaluation of the third lipoprotein component remaining on the starting-point, since this could not be fully separated from the β-lipid

As most workers dealing with paper electrophoresis admit that this method in practice enables them to separate only α-lipid from the whole lipoprotein complex, this modification of the paper electrophoretic technique seems advantageous This procedure, however, makes it impossible to follow some details of lipid abnormalities—e g, of the pre-β-lipid band—that may be of significance in patients with peripheral- and coronary-artery diseases

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D WIEDERMANN

PATIENTS' RECORD CARDS

SIR,—There are some measures which if taken solely for reasons of economy might also benefit the patient and raise the standard of medicine There is now too much duplication of secretarial work because the ways of giving information to the family doctor differ between hospitals, clinics, and medical officers of health, and there is at the moment no method which is particularly convenient for the family doctor or which enables him to have a summary of hospital investigations on one card and a list of vaccinations and immunisations on another The present administration at hospitals often compels a patient to attend an outpatient department unnecessarily in order to ensure that a family doctor obtains necessary information, and should the patient not attend an appointment the family doctor is left without information Patients may be referred from one hospital department to another because there is no clear way of showing that other investigations have already been carried out and where further information about them may be obtained

Most family doctors entrust their patients with a letter to be given to the consultant to whom they have been referred Maternity patients are trusted still further to carry with them a card on which is written the results of blood-tests and progress notes The family doctor, the obstetrician, and the midwife all contribute as a team to these notes In this way much secretarial work, stationery, and postage is saved, and at the same time doctors and nurses are learning from the observations of each other and the patient quickly comes to realise the interdependence of doctors and nurses wherever they work This is perhaps the reason why these notes rarely get lost If this did happen a duplicate could be made from other records kept at hospital and by the family doctor The family doctor at the end of the confinement keeps the medical card that was carried by the patient and he has no need of any further information The card fits the patient's record folder kept by him and thus the whole history of the pregnancy is more readily seen than even one folded hospital letter

The medical officer of health might use a card of a standard size on which would be recorded vaccinations of infants performed at clinics, and this card would be sent to the family doctor after his own health records were completed Should the family doctor carry out subsequent immunisations the card could be taken to the medical officer of health to be stamped as evidence of notification It would be returned to the patient's record envelope so as to be readily accessible and near where the patient lives

A family doctor sending a patient to hospital could enclose with his letter a similar card devoted to past hospital attendances If the patient were being sent for routine investigations the consultant might signify his agreement on the card and add the results on it as they became available The patient would be allowed to carry the card between one doctor and another The consultant would send a letter to the family doctor at the end of the investigations A patient attending a hospital over long periods would have significant findings added to his card as they came to light, and thus the number of hospital letters would be reduced and those that were written would be a commentary of a period of treatment illustrated by the hospital card In order to save a patient attending hospital merely for the result of an investigation, the card would be retained by the consultant and would be a reminder that information had not

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1 Dagnall, P *Lancet*, 1957, ii, 1120
2 Franglen, G *ibid* p 1288
3 Smith, E *ibid* p 910

yet been received by the family doctor The card would then be sent by post after the information had been recorded on it

Nothing should be recorded on the card that would harm the patient should he read it, and the art of letter-writing should flourish where routine observations and acknowledgements would be given in other ways It might be said that the patient might learn too much about his illness, but such an argument loses much of its point in this modern age which provides such information in so many different ways We expect patients to know their weight, their insulin dosage, and blood-groups Is it not a simple stage further to allow a patient undergoing the inconvenience of iron injections to see how his hæmoglobin increases? Patients having hypotensive drugs can often tell the doctor whether the blood-pressure is raised or not, and those who have insisted on being told the recordings can often forecast the amount of the rise or fall with some accuracy

The information on the record cards may be later used by a patient bringing an action in law against a doctor Fear is a bad counsellor, and must not be allowed to over-ride the advantages of an idea which would cut unnecessary expense and waiting-lists and at the same time improve medical record-keeping, for the family doctor is able to retain records for as long as the patient lives

From these notes he might produce valuable findings which would be accepted for evidence of good work on taking higher examinations, and the consultant by reading the family doctor's observations might gain a respect for his opinions outside his own specialty and thus the patient would not needlessly be referred to another department

London, E.17 JAMES H S MORGAN

ALKALINE PHOSPHATASE IN THE WHITE CELLS

SIR,—It is with interest that we read the opinion expressed by Dr Leonard, Dr Israels, and Dr Wilkinson (Feb 8) that the determination of alkaline phosphatase in the leucocytes is at present the best, and often the only, means of distinguishing between myeloid leukæmia and leukæmoid reactions involving the myeloid series of cells Recently we have found this investigation of decisive value in establishing the diagnosis in two cases, using the histochemical method of Wiltshaw and Moloney[1] The absence of alkaline-phosphatase activity confirmed the diagnosis of chronic myeloid leukæmia in the first case though there was no clinically detectable splenomegaly and no initial increase in the leucocyte-count

A man, aged 78, was admitted for treatment of anæmia and congestive cardiac failure His hæmoglobin was 37%, leucocyte-count 10,200 per c mm (neutrophil polymorphs 71%, eosinophils 1%, basophils 3%, lymphocytes 15%, monocytes 7%, metamyelocytes 1%, myelocytes 2%), platelets 177,000 per c mm Marrow (aspiration from sternum) very hyperplastic, myeloid/erythroid ratio 80/1, erythropoiesis normoblastic, the increase in the myeloid series was mainly in the stages of myelocyte, metamyelocyte, and polymorph, no apparent increase in megakaryocytes The leucocyte-count has subsequently increased and the patient is responding to bisulphan ('Myleran') and prednisolone therapy The serum-cyanocobalamin (vitamin B_{12}) content was estimated at 2000 µµg per ml and the serum-uric-acid was 5 8 mg per 100 ml

In the second case[2] the early hæmatological findings suggested the diagnosis of neutrophilic leukæmia, and the appearances in the peripheral blood were similar to those in the case described by Tuohy[3], but an obvious increase in the leucocyte alkaline-phosphatase activity was found

A woman, aged 80, was admitted with anæmia and signs of congestive cardiac failure Her hæmoglobin was 44%, leucocyte-count 63,600 per c.mm (polymorphs 97%, all adult forms seen) The sternal marrow showed evident hyperplasia of erythroid, myeloid, and megakaryocytic elements After four months of treatment with iron the patient became polycythæmic erythrocyte-count 6,880,000 per c.mm, hæmoglobin 117%, packed-cell volume 58%, mean cell volume 84 c µ, mean corpuscular hæmoglobin concentration 30%, and platelets 922,000 per c mm

Now, after a year, during which the patient received no hæmatinics, the hæmoglobin is 85%, leucocyte-count 91,100 per c mm (neutrophils 94%, eosinophils 3%, lymphocytes 1%, monocytes 2%), and the red cells are hypochromic The leucocytes are still only adult forms and have a very high alkaline-phosphatase content The serum-vitamin-B_{12} level is 1000 µµg per ml

This case is an example of a myeloproliferative syndrome in which the salient feature is a leukæmoid blood-picture consisting of marked neutrophilia without immature leucocytes in the peripheral blood The high alkaline-phosphatase level in the leucocytes distinguishes it from true leukæmia

We are indebted to Dr D Mollin of the Postgraduate Medical School, Hammersmith, for the serum-vitamin-B_{12} estimations

Whittington Hospital,
London, N 19

A A CHAZAN
A N EXTON-SMITH

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[1] Wiltshaw, E., Moloney W C *Blood* 1955, 10, 1120
[2] Exton-Smith, A N, Chazan A A *Proc R Soc Med* 1957, 50, 510
[3] Tuohy, E L *Amer J med Sci* 1920 160 18

ADRENOCORTICAL STEROIDS IN MALIGNANT EXOPHTHALMOS

SIR,—In "hyperophthalmopathic Graves' disease" the ordinary features of hyperthyroidism are associated with an inordinate severity of eye-signs, in most cases this type of exophthalmos, we believe, decreases as the thyroid overactivity is brought under control But in "malignant exophthalmos" ("progressive exophthalmos", "exophthalmic ophthalmoplegia") thyrotoxicosis is absent or mild, the most successful remedies appear to be deep X-ray therapy to the pituitary gland and/or orbits themselves or decompressive operations The response to X-ray therapy may not be evident until months later, and it is hard to assess treatment, because the condition tends to fluctuate spontaneously and remit completely Further confusion exists because the distinction between these two types of exophthalmos is not always appreciated.

The reported results of cortisone and corticotrophin have been diverse[1-4] We have experience of high doses of steroid hormones in several patients with malignant exophthalmos None was thyrotoxic, and in all the exophthalmos was considered "malignant" because of the severity of the eye-signs and the progressive course

CASE 1[5]—*A man, aged 48, had rapidly progressive proptosis, lid œdema, and chemosis of the left eye, the right was mildly affected The globe was tense He had diplopia and paresis of external ocular muscles Thyroid function was normal*

Treatment with 350 mg cortisone daily resulted in prompt improvement in œdema and gradual regression of exophthalmos Reduction in dosage (to 100 mg a day) was followed by exacerbation of the signs on several occasions Accordingly cortisone 300 mg a day was continued for about 3 months, followed by prednisone 50 mg a day This was gradually reduced to 20 mg, and 9 months after beginning therapy it was stopped completely 6 months later the eye was quiescent with no return of proptosis

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[1] Chandler, G H, Hartfall S J *Lancet*, 1952, i, 847
[2] Hill, S R., Reiss, R. S, Forsham, P H, Thorn, G W *J clin. Endocrin.* 1950, 10 1375
[3] Medical Research Council *Lancet* 1955, i, 6
[4] Kinsell L. W, Partridge, J W *Ann. intern. Med* 1953, 38, 913
[5] Leftwich, P *S Afr med J* 1956, 30, 309

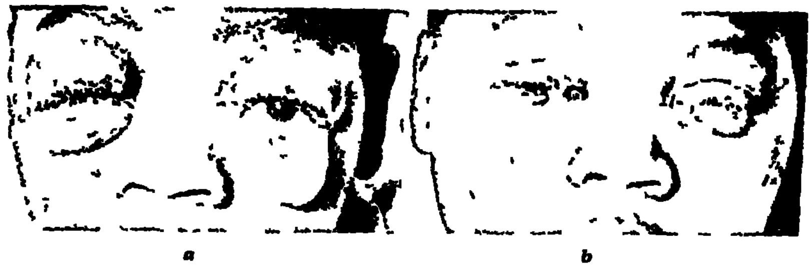

Fig 1—Case 2 (a) Bilaterally affected eyes before treatment (b) After decompression of left eye, and cortisone Note the striking regression of right eye, and cushingoid appearance of face

CASE 2—A boy, aged 14 (fig 1), had for 2 months had pain in the eyes He had gross exophthalmos in both eyes with almost complete ophthalmoplegia, high eyeball tension, and gross lid-œdema and chemosis

Cortisone was given in doses of 800 mg a day, within 48 hours of the institution of cortisone, both eyes had dramatically improved (fig 2) After a few days the dose was cut to 600 mg and a left-sided Naffziger operation [6] was done After 2 months, severe hyperglycæmia necessitated withdrawal of the drug, within a few days severe exophthalmos of the right eye recurred and a right Naffziger operation was performed Postoperatively he had a left iritis, but this was soon controlled, and the diabetic state regressed

CASE 3—A woman, aged 38, had had a thyroidectomy for non-toxic goitre in 1946 She had postoperative hypothyroidism, hypoparathyroidism, galactorrhœa, and exophthalmic ophthalmoplegia [7] The proptosis settled, but the ocular paresis remained, and in April, 1955, the right inferior and superior rectus muscles were resected A year later the right eye became again exophthalmic, red, painful, and oedematous The left eye was less severely affected throughout Prednisone (100 mg a day) was started A response was apparent within 3 days (fig 2), but the condition grew worse as the dose was decreased When on 10 mg a day she noticed that, if the eye became red and watery in the morning, doubling the dose removed these symptoms, they persisted if the dosage was not increased Because of severe side-effects of prednisone a decompression operation was performed on the right eye in February, 1957

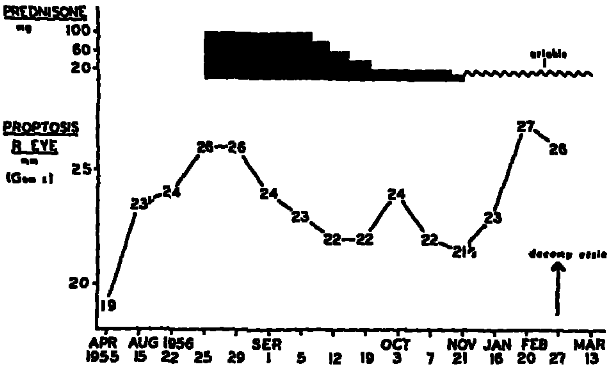

Fig 2—Case 3 Course of proptosis under treatment with prednisone

CASE 4—A woman, aged 55, had developed exophthalmos of the left eye several years previously, a decompressive operation had given a good result 3 months before we saw her, exophthalmos had begun in the right eye (fig 3) This progressed rapidly, and, on admission, was associated with diplopia, ophthalmoplegia, chemosis, gross oedema, and "cementing in" of the eyeball Cortisone was started in doses of 600 mg a day Regression began within 48 hours but when the dose of cortisone was tailed off to 100 mg a day, the right eye rapidly deteriorated and a Naffziger operati was performed Postoperative course w uneventful

This patient had nodular thyroid e largement, but function was normal

CASE 5—A woman, aged 60 6 mont before admission her left eye became r and the vision slightly blurred, a little lat it "swelled" There was never pain n even discomfort The left eye was pr ptosed and movement slightly diminish in all directions, with complete paralysis abduction There was no diplopia, visi fields were full, acuity 6/12 The right e was normal, except for bilateral hypertensive and diabe retinopathy The patient was euthyroid, but had a sm nodular goitre

The proptosis, ocular tension, and visual acuity rapi worsened (fig 4), the visual fields became grossly contract and movement of the eyeball negligible Chemosis a congestion increased alarmingly The diagnosis was uncert since the proptosis was strictly unilateral and the patie euthyroid

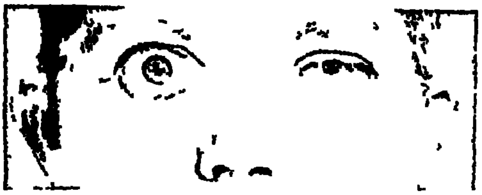

Fig 3—Case 4 Proptosis of right eye, previous decompression left side

We decided on a therapeutic trial of prednisone (100 m daily), carefully watching the blood-pressure and mild diabete Within 3 days of starting prednisone there was great subjecti and objective improvement (fig 4)

The prednisone was stopped after a month, when the le eye appeared completely normal There was no recurren during the next month

Like Kinsell,[1] we found that large doses of adren steroids produced a rapid, even dramatic, response exophthalmos Our experience with long-term thera of this sort has been less happy, but in cases 1 and 5 least, improvement was prolonged

This form of treatment warrants further use It ma be of value as a therapeutic trial of the diagnosis, whe the endocrine origin of the exophthalmos is not cl (e g , case 5), or in tiding the patient over a climax, wh desperation otherwise might force operative interferen It certainly acts more quickly than does X-irradiati In some cases, at least, improvement is "permanent"

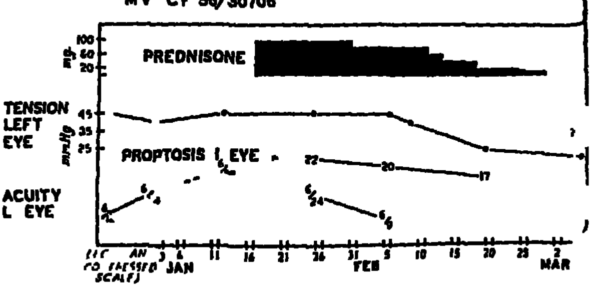

Fig 4—Case 5 Progress of eye under treatment with prednisone

We are pleased to thank Prof J F Brock, Dr S Berman, Dr P Leftwich for permission to report on patients under care, Dr R L H Townsend for referring case 5 to us, and

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[6] Naffziger H C Ann R Coll Surg Engl 1951 15, 1
[7] Jackson, W P U J clin Endocrin 1956, 16, 1215

Forman for his continued interest and encouragement The ffinger operations were performed by Mr de Villiers Hammnn d Mr A Gonsky The expenses incurred in connection with is report are defrayed by a grant from the Council for Scientific d Industrial Research

Endocrine Clinic,
Department of Medicine,
Groote Schuur Hospital and
University of Cape Town

R HOFFENBERG
W P U JACKSON

ORDER AND DISORDER IN THE CEREBRAL CIRCULATION

SIR,—Sir Russell Brain [1] quotes the investigations of awrence and Rewell [2] into the cerebral circulation of the iraffe These workers suggested that in the giraffe blood ight be shunted from the carotid artery into the vertebral tery, with which the carotid communicates freely, and at this shunt would protect the brain of the giraffe from cessive hydrostatic blood-pressures

We have recently published our findings [3] in this ecies, and have shown that the rete mirabile is supplied the vertebral artery The connection was demonstrated dissection and by angiography If these findings are cepted, then Lawrence and Rewell's hypothesis falls ay It was in any case difficult to understand why ood should shunt from one large artery into another, which the blood-pressure would presumably be nilar There is no proof of any shunt mechanism in is animal

To make their suggestion more plausible, Lawrence d Rewell had postulated that the giraffe would be found have a high blood-viscosity This has also not been rified in previous observations from this laboratory [4]

We have suggested [3] an alternative means by which the rebral circulation of the giraffe may be adapted to the avitational effects caused by changes of posture in this imal

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E N KEEN

niversity of Cape Town

YDROXYDIONE IN DEHYDRATED PSYCHOTIC PATIENTS

SIR,—Since hydroxydione ('Viadril') seemed a very e drug (its L D $_{50}$ is three times that of thiopentone), one us (D E M) suggested its use as a general sedative in turbed patients, since it must be given intravenously dilute solution, disturbed dehydrated psychotic tients seemed particularly suitable

5 g of hydroxydione was dissolved in 500 ml of sterile glucose saline solution Two drip sets were used A cose saline drip was started, and the needle of a hydroxydione p was inserted into the lumen of the lower part of the rubber bing of the first drip and secured by adhesive Each drip was ntrolled independently by a screw clip This ensured that the transfusion channel was functioning properly before the droxydione was used, thus diminishing the risk of tissue crosis, (2) the solutions could be used independently or gether, and (3) the transfusion channel would not become ocked on change-over from one solution to the other

The hydroxydione solution was given at 150 drops a minute til the patient fell asleep, it was then turned off and the ucose saline drip turned on The hydroxydione was restarted the same rate when the patient began to show signs of restsness, until he again fell asleep

Six patients were treated—three with senile psychoses, one th paraphrenia, one with status epilepticus, and one with lirium tremens All were successfully kept asleep for periods nging from 2 hours to 3 days, during which 1–7 litres of fluid was infused No ill effects were seen, the blood-pressure fell in four cases, but not dangerously Four patients recovered and were able to eat Two later died, one (who had had a hæmatemesis before treatment) of bronchopneumonia, and the other with a recurrence of status epilepticus

All these patients were seriously ill, dehydrated, and difficult to nurse During sedation with hydroxydione for varying periods, very necessary fluid was given with comparative ease

Stanley Royd Hospital,
Wakefield

D E MUNRO
D A KNOX

RADIATION, LEUKÆMIA, AND MALIGNANT DISEASE

SIR,—The suggestion of Dr Alice Stewart and her colleagues [1] that antenatal X-ray examinations may cause malignant disease and leukæmia in the child has been ably refuted by your correspondents,[2-5] but the growing publicity that this hypothesis has obtained and the widely expressed fear of diagnostic irradiation that it has encouraged demand further action This should be your duty because of the uncritical enthusiasm with which you endorsed the preliminary communication in a leading editorial [6] Your editorials are so influential that no argument in your correspondence columns can outweigh them with most readers, and although you are not expected to act as a referee in all such arguments, in this case, because of your original attitude, you are morally bound to express a further opinion When you do so may I suggest that you emphasise the following points?

Stewart et al [7] have agreed that "Dr Reid is justified in stressing that, on the evidence of our figures, over 90% of cases of malignant disease in children under 10 years of age (which are in any case rare) must be due to causes other than diagnostic irradiation" In the less than 10% of cases in which the children were irradiated antenatally these other causes could not be excluded, and the probability is that the same incidence of "other causes" would have been operative in this group The absurdity of postulating diagnostic irradiation as a possible cause becomes manifest when this argument is applied to the remaining less-than-1%

The controls used in this work were inadequate [2-5 8] Stewart et al did not deny their inadequacy, instead they stated [7] "as previously reported, a higher incidence of antenatal irradiation is still found among our cases when comparison is restricted to controls of corresponding parity" Unfortunately, reference to the letter they quote [9] does not appear to substantiate this statement, for therein appears "they were deliberately *not* matched for birth rank", and "*I am not at the moment in a* position to quote parity figures for the mothers included in the preliminary report", and the controls remain nebulous and inadequate

The figures given by Stewart et al do not show, as they claim, "that the child population dying of leukæmia and cancer nowadays includes a disproportionately large number of first-born and twins", nor is there evidence that matching for birth rank would have obscured this information if it were present Indeed, such matching would have provided a sounder basis for attempting to evaluate the part played by diagnostic antenatal irradiation than Stewart's inability to think "why, when first conceived, first-born children should be more likely to develop leukæmia or cancer than other children" [9] There was a time when people could think of no other reason than the evil eye

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[1] Brain, R *Lancet* 1957 ii 859
[2] Lawrence, W E Rewell R E *Proc Zool Soc, Lond* 1948, 118, 202
[3] Goetz, R H Keen E N *Angiology* 1957 8 542
[4] Goetz R H, Budtz Olsen, O *S Afr med J* 1955, 29, 773

[1] Stewart A Webb J, Giles D, Hewitt, D *Lancet*, 1956, ii, 447
[2] Rabinowitch J *ibid* p 1261
[3] Rabinowitch, J *ibid* 1957, i, 219
[4] Reid, F *ibid* p 428
[5] Sonnenblick B P *ibid* p 1197
[6] *ibid* 1956 ii 449
[7] Stewart, A, Webb J Giles, D, Hewitt, D *ibid* 1957, i, 528
[8] Ellis, F, Lewis C L *ibid* 1956, ii, 573
[9] Stewart, A *ibid* p 573

The suggestion that individual twins received significantly different doses of antenatal irradiation is baseless speculation In the 10 years under review an antenatal X-ray examination often included several views—e g , anteroposterior, postero-anterior, lateral, and both A-P and P-A half-axial (Thom's and Chassard-Lapine's) views—and my guess (as good as Stewart et al 's) is that the individual twins would not have received greatly different doses What do Stewart et al mean by "a *disproportionately* large *number* of first-born and twins"? In proportion to what? Did they consider that the risk of malignancy per pregnancy must be at least twice as high for twins as for singletons because there are twice as many children per pregnancy?

In any case, even if we accept that these diseases and antenatal X-ray examinations are commoner in twins and in the first-born it does not follow that there is a causal relationship Huff [10] warns "The post-hoc variety of pretentious nonsense is another way of changing the subject without seeming to The change of something *with* something else is presented as *because of*" This post-hoc-propter-hoc argument is particularly inapplicable in a case such as this, where diagnostic irradiation is extremely common and the alleged sequel extremely rare, and furthermore, where the same disease is known to occur as the result of other causes in at least 90% of cases

Apart from the unsatisfactory method of the selection of the controls, the method of the collection of the information is open to question, and there is no evidence that the object of the interviews was hidden from the interviewing doctor or from the subject interviewed Moreover, a slight bias could be introduced by the fact that a mother of a child dead of malignancy would have recalled the incidents of that particular pregnancy many times, and would only too readily catch the idea that an X-ray examination may have been responsible The incidents of a first pregnancy would also be more readily recalled But the incidents of later pregnancies with normal children would not be as likely to stimulate the memory This bias, however, may not have affected the results materially, and in view of the fundamental fact of the inadequacy of the control group, it may not even be important at all Perhaps more important is the possibility of unconscious bias in the authors This one cannot fail to suspect Mr Hewitt has already contributed to the study of leukæmia in relation to ankylosing spondylitis and X-ray therapy Without minimising this achievement, one cannot but wonder whether in the work being discussed here he merely found what he sought The ease with which the authors attribute leukæmia and malignant disease to X-ray examinations because they can think of no other reason, their unquestioning acceptance of the significance of the word "routine" on an X-ray request form, and the important apparent contradiction (noted above) in their evidence also seem to point to bias

The work of Stewart et al has assumed the importance that you attributed to it as "the first published epidemological evidence of the hazards of diagnostic radiology to the patient" [6] As such it deserves re-valuation by you without reference to other speculative extrapolations from massive doses of irradiation in man and in experimental animals, for there is no other relevant suggestion that these can be compared with the doses obtaining diagnostic procedures

You would be rendering a service to the profess and to the public if you would persuade Dr Stew and her colleagues to publish the full results of t survey, of which we have had, after 18 months and spite of its alleged importance and wide publicity, o the preliminary report

Johannesburg HARRIS JACKSON

*** We have no regrets about publishing the prelim ary communication by Dr Stewart and her colleagu we see it as one of our functions to make known as so as possible those findings which, we judge, may turn to be of crucial importance By our remarks at the ti we sought to draw attention to the possible significa of these preliminary results we did not endorse a particular conclusion that might be drawn from the We have shown Dr Jackson's letter to Dr Stewart a we are glad to learn from her reply, which follows, t the final report on the survey is nearly complete W await with interest an opportunity to reassess the situ tion —ED L

SIR,—Like Dr Jackson, we regret the length of ti which has elapsed between our preliminary communic tion and the appearance of a full report This delay h resulted from the unusually large scale of the survey a the fact that we have studied a number of other topi besides fœtal irradiation In the meantime we have alwa given the fullest available information to anyone who w sufficiently interested to write to us direct

Dr Jackson's criticisms are of the most general ki and cannot be answered adequately in a letter In o final report we shall deal with the possibilities of err arising from imperfections in the selection of controls an from bias in the mothers' reports As this report is no nearly complete and should be in print shortly, we woul ask readers who share Dr Jackson's scepticism to suspen judgment until they have seen the evidence in full

ALICE STEWART
D HEWITT
J W WEBB

Department of Social Medicine,
Oxford University

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—Had Dr Ryle, in his letter last week, been able t suppress part of his personality (it would have been to soon to have expected a change) he would not hav revealed himself as such an unscientific observer b attributing statements to me which I never made

The point at issue is this In the past doctors have no thought it worth while to investigate functional disorders partly because the scientific instruments in use always gav negative results Today the position has changed, thes disorders are being subjected to scientific inquiry and th main instrument used is the psychiatrist's own mind Ju as the scientist recognises and allows for the errors of th scientific instruments he has fashioned, so the psychiatris must recognise and allow for the errors of his own min if he attempts to use it as a scientific instrument I learning to recognise the errors of his mind, the psychia trist undergoes some personality change, for, in seein himself at times as others see him, he becomes less boun by his previous pattern of behaviour and more receptiv to the behaviour problems of his patients

Scientific inquiry has shown that the psychoanaly cannot practise his specialty without undergoing a ysis himself, and recent research suggests that the eral practitioner cannot attempt similar work in a ted field without undergoing some modified analysis ersonality change It has been found that general titioners can effect this change by regular attendance minars dealing with the psychiatric problems of their ents

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[10] Huff, D How to Lie with Statistics, p 135 London, 1954

ndon, W 8 H STEPHEN PASMORE

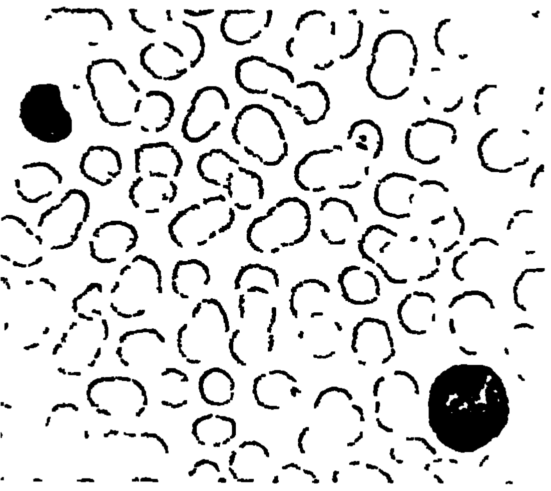
IR,—Dr Ryle (March 22) is surely correct that in er to carry out psychotherapy in general practice it is necessary for the family doctor to " make a personality nge " This idea derives from Dr Balint's book,[1] but ently when I asked Dr Balint about this, he agreed he meant only a change in approach on the part of doctor to his patients' problems and a better understanding of the part which the doctor himself plays in doctor-patient relationship Not even two years' ndance at a Tavistock Clinic seminar would produce asic personality change in the doctor

Mary Cray, Kent. E TUCKMAN

STAINING FOR LEUCOCYTE PEROXIDASE

IR,—The use of benzidine as a laboratory reagent is idly becoming a thing of the past. Those engaged in manufacture are exposed to the risk of carcinogenesis l for this reason it is no longer being produced lidine provides a satisfactory substitute, and has n used for some time in testing for occult blood in es[2]

Then blood-films are stained for leucocyte peroxidase vity, benzidine may be replaced by *o*-tolidine, and there little difference in the final appearance of the film Using ashburn's method of staining,[3] the reagents are



tion 1	*o*-Tolidine	0 3 g
	Ethyl alcohol	99 ml
	Sodium nitroprusside (saturated solution)	1 ml.
tion 2	Six drops of twenty-volume hydrogen peroxide solution in 25 ml water	

The accompanying figure shows the appearance of a roxidase-positive and a peroxidase-negative leucocyte, ng this method with a Leishman counterstain.

Department of Clinical Pathology,
Charing Cross Hospital Medical School,
London W C.2

ALLAN JACOBS

Balint, M The Doctor the Patient, and his Illness London, 1957
Kohn, J, O Kelly, T *J clin Path* 1955, 8, 249
Whitby L. E. H Britton, C. J C. Disorders of the Blood London, 1957

BASAL METABOLIC RATE IN THYROTOXICOSIS

SIR,—We were very pleased to see the interesting paper by Professor Wayne and his colleagues (March 22) Their results so completely agree with those obtained at the West London Hospital during a three-year period that we should like to bring these to your attention We have used Robertson's technique[1] for determining the B M R (barbiturate sedation was not used) and the standards of Robertson and Reid[2]

—	Crooks, Murray, and Wayne		Goldberg and Seaman	
	Euthyroid	Thyrotoxic	Euthyroid	Thyrotoxic
No of patients	73	136	237	95
No of patients having non-confirmatory B M R results	9 *(12 3%)*	16 *(11 8%)*	32 *(13 5%)*	11 *(11 6%)*

Comparable results are shown in the accompanying table

West London Hospital
Medical School,
London, W 6

I J L GOLDBERG
M J SEAMAN
E K BRUCK

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

SIR,—No conclusion whatever can be drawn from the data presented by Dr O'Connor last week Of his 18 patients, most or all (it is not clear which) were taking primidone or diphenylhydantoin, or both, at the same time as 'Spansule' phenobarbitone, and some were having their doses of diphenylhydantoin increased, credit for improvement cannot be assigned to any one of those drugs separately There can be no guarantee that the patients took their various anticonvulsants as regularly before the spansule period as they did during it. Much or all of the " improvement in personality " may have been due to added interest shown in the patients during this stimulating trial Since fits occur especially at times of bodily inactivity and mental vacuity, this added interest and stimulation may have helped to reduce their frequency

Eighteen is too small a number of cases The only valid kind of test of such a method of treatment would be a double-blind controlled clinical trial, planned with advice from a medical statistician Dr O'Connor's results are striking indeed, but others hardly less striking have been overthrown by controlled trials, good examples being those of Kurtzke and Berlin[3] and Booth et al[4] He will have to begin again

London, W 1 JOHN PENMAN

SIR,—Dr O'Connor's article comes opportunely at a time when it seems that, in children at least, phenobarbitone is responsible for as many symptoms as it alleviates The personality changes described are most encouraging, and I hope that Dr O'Connor or someone else will soon be able to repeat this work with children who are receiving phenobarbitone only So many other forms of treatment were being given, besides the doubling of the daily dose of phenobarbitone, that some of the improvement observed may have been due to something other than the method of

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1 Robertson J D *Brit med J* 1944 i, 617
2 Robertson J D Reid D D *Lancet*, 1952, i, 940
3 Kurtzke J F, Berlin, L *Amer Rev Tuberc* 1954 70, 577
4 Booth C. B, et al *J Amer med Ass* 1957, 163 168

administering phenobarbitone, and it is most important that the success of this treatment should be confirmed as quickly as possible

Lewes, Sussex DENNIS PIRRIE

ADRENALINE CREAM

SIR,—The rationale for the treatment of muscular rheumatism with adrenaline cream, which I first advocated ten years ago, was criticised on five counts

(1) Adrenaline could not be stabilised in a fatty base

(2) It could not penetrate the skin

(3) Even if it did so the amount would be too small to be effective

(4) If it did have any effect it would *reduce* the blood-supply to the muscles because it would constrict the arteries supplying them and not expand them, as I claimed

(5) There was no anatomical or physiological evidence for the claim that much of the pain of muscular rheumatism emanates from "trigger-spots"—localised areas of muscle in spasm

It can now be justly claimed that all these criticisms are unfounded

(1) Pharmaceutical tests specially devised for the assay of adrenaline cream have proved it has a substantial shelf-life

(2) By histochemical methods, Bourne[1] has demonstrated that adrenaline in a fatty base penetrates living skin rapidly

(3) Work at the National Institute for Medical Research proved that the action of adrenaline on the arterioles[2] of skeletal muscle is peculiar in that it relaxes them The concentrate required to produce this effect is astonishingly small

(4) Bonica[3] has confirmed the existence of trigger spots and their responsibility for rheumatic pain Other authorities[4 5] have expressed their agreement

The few and, in my opinion, perfunctory clinical trials of adrenaline cream have given equivocal results but it can surely be claimed that criticisms of the rationale, and particularly against the claim that adrenaline can penetrate the skin, are unjustified

London, W 1 LOUIS MOSS

LEG SUPPORT FOR USE DURING VAGINAL OPERATIONS

SIR,—I was interested in Dr Goodwin's letter of March 8 criticising the type of leg support which I had previously described,[6] and I should like to comment on his remarks

The abduction of the thighs is obtained without any obvious lordosis, but it is part of my design that this abduction can be varied to suit the operator's requirements, and it can be reduced to any required degree

The popliteal vessels are not compressed by the canvas support, as this is quite effective when it reaches only half way up the calf of the leg With regard to the access by the assistant to the field of operation, I have repeatedly asked those who help me their opinion about this, and I am told that they find this no difficulty and even welcome the support of the strut to lean on without actually putting their weight on the patient's leg

Mr Goodwin's photographs show very clearly those points which I have endeavoured to avoid, particularly with regard to excessive flexion of the hip-joint This flexion predisposes to thrombosis and backache, and my anæsthetist dislikes it because the pressure of the thighs on the abdomen serio interferes with respiratory movements

I have the advantage of having worked with the typ support illustrated by Mr Goodwin as well as my own, I think if he is able to make a similar practical comparis he will agree that the design I have suggested has cer definite advantages

General Hospital,
Ashton-under-Lyne T B FITZGERALD

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1 Bourne, G H *Nature, Lond* 1957, 180, 1488
2 Swan, H J C *Brit med J* 1952, i, 1003
3 Bonica, J J *J Amer med Ass* 1957, 164, 732
4 Davis, P S *Med Pr* 1957, 238, 77
5 Dittrich, R J *J phys Med* 1957, 20, 233
6 *Lancet*, 1957, ii, 577

Medicine and the Law

Death from Barbiturate and Alcohol

IN 1956, 223 people died in England and Wales accidental barbiturate poisoning—compared with only ten years previously Death may result from a moder dose of barbiturate if alcohol is taken as well[1] This w shown again at a Sutton inquest on March 18[2]

A man, aged 50, had been under heavy pressure of w and, according to his family doctor, insomnia had been "a c siderable problem" to him, he was accustomed to taking up four capsules a night of a barbiturate, which his doctor agre was a fairly heavy dose He was found dead in bed one mor ing, and analysis of his stomach contents indicated that he h taken only his usual dose of barbiturate, but a bottle of whi bought the previous night was only a quarter full, and housekeeper said she had never known him drink as mu before The coroner said that it was not as generally kno as it should be that a dose of barbiturate that was not norma fatal might be fatal if taken with alcohol

A previous inquest indicated that methylpentynol also dangerous in conjunction with barbiturate[3]

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1 See *Lancet*, 1953, i, 1140, *ibid* 1953, ii, 554.
2 See *Liverpool Daily Post*, March 19, 1958
3 See *Lancet*, 1955, i, 1332

Parliament

QUESTION TIME

Persomnia

Mr JOHN RANKIN asked the Minister of Health if he w aware of the growing feeling in medical circles that 'Persomn should not be on free sale across the counter but only on t prescription of a registered medical practitioner —Mr DER WALKER-SMITH replied I am aware of the publicity that h been given to this preparation and of its alleged abuse in certa cases I have no official reports upon it, but I am consulti with the Home Secretary as to whether a further reference the Poisons Board of bromvaletone and carbromal, the princip ingredients concerned, would be desirable in the light of su general information as is now available

Refunds for Prescription Charges

In six years some £3,200,000 for prescription charges h been refunded through the Post Office to needy persons

Appointments

PINKERTON, J R H, M D Cantab consultant pathologist, Boston group hospitals, Lincolnshire
SHARPE, OLIVE, M D Sheff, M R C P, D C H consultant pædiatrician, Roy Liverpool Children's Hospital

Colonial Appointments:

ATKINSON, P I, M B Calcutta M O, Northern Region, Nigeria
BRAHMAN, A P, M B Madras M O, British Guiana
CHICK, J H, M B M O, Tanganyika
DIGGORY, H J P, M B, D T M & H M O (grade C), Trinidad
DONNELLY, J P, L R C P I M O (grade B), Institutions, Trinidad
MOITRA, N G, M B Rome, D M R E radiologist, Trinidad
SLAWINSKI, KAROL, M D Beirut, T D D M O, Sarawak
WATTS, M B M B Lond, D OBST, D C H M O, Sarawak

Obituary

HENRY CODDINGTON BROWN

C I.E , B.A., M.B Cantab , D T.M & H.

ajor H C Brown, who died on March 18 at the age 1, will be remembered by colleagues in India and in country for his work as bacteriologist at the Central earch Institute, Kasauli, and at the Wellcome Labora- es in London

e was born in India and came of a family which gave dis- shed service to that country Educated at Dulwich ege, Emanuel College, Cambridge, and St. Thomas's spital, he rowed for his college and represented his hospital water-polo

oon after qualifying in 1902 he joined the Indian Medical vice and, after service on the North West Frontier and in na as a regimental medical officer, he became bacteriologist assistant director of the Central Research Institute, Kasauli ing the 1914–18 war his department was responsible for the paration of vaccines for the Indian troops fighting in the ddle East, and it was at this time that he worked out the thod which is still in use of estimating the number of anisms in a bacterial suspension by comparison with a series ubes of graded opacity

He left the I M.S soon after the end of the war and was pointed bacteriologist at the Wellcome Bureau of Scientific search, London (now the Wellcome Laboratories of Tropical edicine) After he left this post in 1940 he worked for some ars, part-time, at the Leishman Laboratory, Aldershot, before iring first to Budleigh Salterton and finally to Camberley e is survived by his wife, a son, and a daughter

J C B writes

Brown was mainly interested in the electrical charges carried bacteria and protozoa, with particular reference to the nges brought about by the action of immune serum and salts high valency This work excited little comment at the time, t its value has been increasingly appreciated in recent years 1922 he was associated with Sir Philip Manson-Bahr and the e C M. Wenyon in diagnosing the first case of Weil's disease gnised in England, and thereafter he made a series of studies the epidemiology of that disease, and on serological methods diagnosis

He greatly enjoyed the society of his fellows, he had a fund of musing reminiscences, and specially enjoyed recounting epi- odes that told against himself He made an admirable colleague, asy to work with, always ready to listen to the opinions of ounger men, and generous in his apportionment of credit to ny who collaborated with him.

Diary of the Week

MARCH 30 TO APRIL 5

uesday, 1st

oyal Society of Medicine, 1, Wimpole Street, W 1
8 P.M *Orthopaedics* Mr John Cholmeley Hallus Valgus (Presidential address)

stitute of Laryngology and Otology, 330, Gray's Inn Road, W C.1
5.30 P.M Prof F C. Ormerod Pathology of Internal Ear

est End Hospital for Neurology and Neurosurgery, 91, Dean Street, W 1
5 30 P.M. Dr E H Larkin Physical Treatment and Psychiatry

ednesday, 2nd

oyal Society of Medicine
5 15 P.M. *History of Medicine* Dr K. Bryn Thomas James Douglas of the Pouch.

stitute of Psychiatry, Maudsley Hospital, Denmark Hill, S.E.5
4.30 P.M Dr H I Weinstock (New York) Statistical Evaluation in Psychoanalysis

idland Medical Society
8 15 P.M (36, Harborne Road Edgbaston, Birmingham, 15) Mr Hugh Carson Hospital Developments (Valedictory address)

anchester Medical Society
4.30 P.M (Medical School, University of Manchester) Prof L N Pyrah Renal Calculus

Notes and News

PHYSICS AND PHYSIC IN GLASGOW

THE clinician, busy with the sick, often dreams of doing research, and hospital physicists do the same Dr J M A Lenihan, in his entertaining report as regional physicist to the Western Regional Hospital Board in Scotland, writes "The main function of the department is not to produce new knowledge but to help the sick in more immediately obvious ways"—by teaching, construction and repair of instruments (including audiometers), and help in the clinical use of isotopes But research is done the projects include a means of summoning staff by radio, and a comparison of the arsenic content of hair in smokers and non-smokers (as an index of the relative intake) by means of activation analysis—i e., neutron bombardment followed by study of the induced radioactivity The department has also made some investigations into radioactive fall-out The physics department has built an end-window Geiger counter, specially suitable for a pure β-emitter such as ^{90}Sr, and in cooperation with the food science department has compared the ^{90}Sr content of dried milk prepared before 1954 (negligible) and of later samples (up to 10 strontium units) A larger programme, involving tests of milk and grass, is in progress

Man irradiates his fellows not only by firing bombs but in the more innocent techniques of diagnostic and therapeutic radiology, and radiation control is an important part of the physics department's work The X-ray-therapy machines in six hospitals are calibrated daily or weekly, and the department assists in planning radium treatment It also monitors the region's 400 radiation workers for radiation dosage by means of film badges Of 1000 consecutive reports, the weekly dose level was under 0 025r in 565, and over 0 3r (the upper limit prescribed in the Code of Practice) in 16 In a quarter of a group with excessive exposures, the film had been separated at some time from the supposed wearer "These figures", comments Dr Lenihan, "give no cause for alarm but they indicate room for improvement" The exposures varied greatly from one department to another, the hazard was in general well controlled in diagnostic departments, but "the equipment generally available for the storage, preparation and transport of radium is seriously inadequate by current standards" During the Glasgow mass-radiography campaign of March-April, 1957, when 700,000 examinations were made, often in conditions far from ideal, no unreasonable radiation hazard was found—70% of the films returned indicated doses less than a third of the tolerance level—but doses were higher, on the average, than those found in hospital X-ray departments Measurements of the radiation received by patients were to start this year

Another service to X-ray departments is the "lucrative and entertaining process" of silver recovery—though in some departments the return is moderate because of "agreements made some years ago with astute contractors"

RADIOTHERAPY UNIT AT WIRRAL

TODAY, Friday, Lord Cohen of Birkenhead is to open a radiotherapy unit at Clatterbridge Hospital, Wirral, Cheshire, which houses one of the five new linear accelerators, operating at a tension of 4-5 million volts, ordered by the Ministry of Health for selected radiotherapy centres The new unit is an extension of the Liverpool Radium Institute Besides providing the accelerator, the Ministry is paying for the ward units, which have been adapted from a wartime American hutted hospital to provide 63 beds The walls of the treatment room are of a special high-grade concrete, varying in thickness between 2 ft. 6 in. and 4 ft. 6 in Both the treatment table and the beam can be moved during treatment to make possible both rotation and arc therapy A wider range can be secured by moving the floor or moving the table laterally on rails The treatment planning room contains special X-ray apparatus for determining precisely the direction and size of the treating beam It includes a planigraph, which can take a radiograph of a transverse section of the body The radiographer can observe the patient under treatment by means of mirrors and talk to him through a two-way sound channel There is a minor operating-theatre for radium insertions

CHANGE IN CORTICOTROPHIN PREPARATIONS

REVISED methods of assay of corticotrophin (A C T H), to be adopted after March 31, necessitate changes in unitage and labelling In most of the assays the drug will be given subcutaneously, and the preparation will be labelled "not for intravenous use" The dose needed to produce a given effect by the subcutaneous or intramuscular route will be unchanged, in terms of units But material for intravenous use (labelled "for intravenous use only") will have to be prescribed in about three times the number of units formerly used to produce a similar effect

Hospitals will be able to order their supplies direct from the manufacturers, and the preparations may be prescribed on form E C 10

A PROCTOLOGY JOURNAL

IN Britain proctology is no more than a special interest of some general surgeons, but in America it is regarded as a specialty of sufficient importance to engage the undivided attention of those who practise it. The American Proctologic Society was founded at the beginning of the century, but while newer specialties have established their own journals, the proctologists have had to remain mute or to find an outlet in more general journals At last, mainly through the exertions of the American Proctologic Society, a new journal has been born—*Diseases of the Colon and Rectum*—under the editorship of Dr Louis A Buie[1] It has been a guiding principle of the society that the interest of those engaged in the specialty should not become too circumscribed, and the subject matter of the first issue of the new journal indicates that this commendable intention is to be its guiding policy Furthermore a flavour of internationalism is notable in the authorship of the original articles Of especial value are the selected abstracts and a comprehensive list of articles on colonic or rectal disorder published elsewhere

University of Leeds

At recent examinations the following were successful

M D—G W Lewis
M B, *Ch B*—R M Hind, M P Wootliff

University of Manchester

Dr J C Denmark has passed part II of the examination for the D P M

University of Sheffield

The title of director of clinical studies has been conferred on Dr I B Sneddon, lecturer in dermatology and secretary of the clinical committee of the faculty of medicine, and of honorary lecturer in psychiatry on Dr F J S Esher

Royal Society

The 25 newly elected fellows of this society include

Mr M Abercrombie, reader in embryology in the University of London at University College, Dr E P Abraham, a senior research officer, Sir William Dunn School of Pathology, University of Oxford, Dr J R Baker, reader in cytology, University of Oxford, Miss Edith Bulbring, university demonstrator in pharmacology, University of Oxford, Dr R K Callow, research chemist, National Institute for Medical Research, London, Dr F J Fenner, professor of microbiology, Australian National University, Canberra, Dr Alexander Haddow, professor of experimental medicine in the University of London and director of the Chester Beatty Research Institute, Institute of Cancer Research, Royal Marsden Hospital, Dr A St G J McC Huggett, professor of physiology in the University of London at St Mary's Hospital Medical School, and Dr J E Smith, professor of zoology, Queen Mary College, London

University of Bristol

Dr R St J Buxton has been appointed lecturer in phy
logy and Dr P T Smith demonstrator in pathology

Royal College of Surgeons of England

The tenth anniversary dinner of the Faculty of Anæsthet
was held at the college on March 19 The dean, Dr Fra
Evans, announced that a chair of anæsthesia was to be est
lished at the college and that Dr R F Woolmer, pre
director of the department of anæsthetics, would be its
occupant The British Oxygen Co had endowed the chai
perpetuity with a gift of £150,000 This, Dr Evans decla
was another magnificent example of the farsightedness
industry and commerce in recognising the need to sup
research He also spoke appreciatively of the great volum
work that Dr Woolmer and his colleagues had accomplishe
quickly in their department Among the guests were the So
ambassador, Mr Jacob Malik, and three noted Russian
geons visiting this country, Prof B A Petrov, Prof V
Pshenichnikov, and Prof I S Zhurov Sir James Pate
Ross, president of the college, welcomed them in confi
Russian and, to mark the occasion, presented each of the
geons with a book Professor Petrov said that Russian surge
had always had great respect for their British colleagues
their work, and be recalled how in 1943 the honorary fellow
of the college had been conferred on Prof S S Yudin, wh
work he was now carrying on As a finale, Professor Pe
allowed himself a few rousing words in his own tongue,
these Dr A J E Duddington promptly interpreted as "L
may the friendship between British and Soviet surgeons
anæsthetists flourish, long live the British and Soviet peop
The Minister of Health, Mr Derek Walker-Smith, prop
The Faculty ("young in years, old in respect and achieveme
and the dean responded In making The Guests feel at ho
Dr G S W Organe hoped that many more visitors would c
and go between Russia and Britain The response for the gu
came from the Lord Mayor of London, Sir Denis Trusc

Prof W Mayer-Gross is to give the Adolf Meyer lecture a
1958 annual meeting of the American Psychiatric Associatio
San Francisco

A postgraduate course in pædiatric surgery, organised by
Evelina Hospital and the Department of Child Health of G
Hospital, is to be held in London at the Evelina Hospital, on S
day, April 19 Further particulars will be found in our advertise
columns

The Central Council for Health Education is holding an i
national seminar on health education at Froebel Educational I
tute, Roehampton Lane, London, S W 15, from April 22 to
Lieut-General Sir Bennett Hance, president of the medical b
of the Commonwealth Relations Office, will give an ope
address on the fundamental nature of health in community deve
ment Further particulars may be had from the medical direct
the council, Tavistock House, W C 1

The College of General Practitioners has set up temporary h
quarters at 41, Cadogan Gardens, London, S W 3 (Sloane 8333)

The annual general meeting of the Auxiliary Royal Army Me
Corps Funds will be held at 11, Chandos Street, London, W 1
Monday, March 31, at 5 P M

The spring dinner of the Wessex Rahere Club will take pla
the White Hart Hotel, Salisbury, on Saturday, April 19, at
request of members in Eastern Wessex Any Barts grad
will be welcome to dine and are asked to write to the hon secre
Mr A Daunt Bateman, 11, The Circus, Bath, Somerset

The London Medical Orchestral Society will give a concer
aid of the Jack Buchanan Cancer Fund, at the Royal Colleg
Surgeons, Lincoln's Inn Fields, London, W C 2, on April 2
8 P M Tickets (£1 1*s*, 12*s* 6*d*, and 7*s* 6*d*) may be had fro
secretary, 6, Oxford Court, W 3

CORRIGENDUM While the late Dr J G Greenfield was worki
Leeds, Matthew Stewart held the appointment of clinical pathol
at the General Infirmary He was not appointed to the chair
1917, when A F S Leyton retired from the professorship o

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Dr. Robert Heilig Library